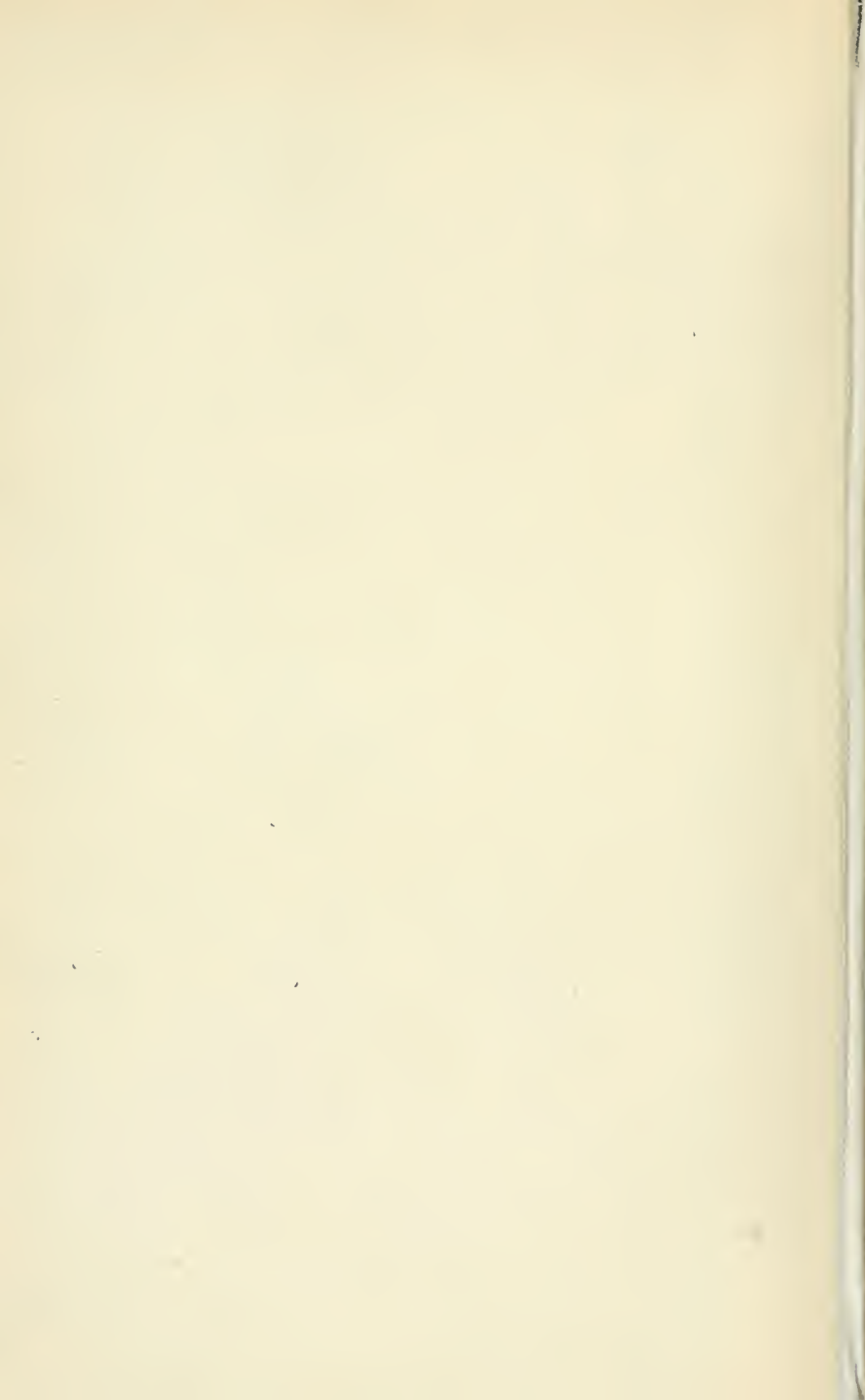


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The Archives of Internal Medicine

Vol. X

JULY, 1912

No. 1

REPORT OF A CASE OF DIABETES INSIPIDUS WITH MARKED REDUCTION IN THE AMOUNT OF URINE FOLLOWING LUM- BAR PUNCTURE *

JAMES B. HERRICK, M.D.

CHICAGO

This case of diabetes insipidus is reported because of the remarkable effect of lumbar puncture in diminishing the amount of urine and raising its specific gravity. A man of 43 had for four years the typical manifestations of diabetes insipidus. The urine varied in amount from 7,500 to 11,000 c.c., and was always of low specific gravity (1.001). Lumbar puncture was made and less than 5 c.c. of fluid withdrawn, the fluid escaping slowly under low pressure. Within forty-eight hours the daily amount of urine had dropped to 660 c.c. Headache, pain in the back of the neck, anorexia and vomiting, with a feeling of general weakness, followed the puncture. Morphin was given for pain. Almost no fluid or food was taken for three or four days. But after the prostration following the puncture had disappeared, when morphin was stopped, and when food and water were freely taken, there was no thirst as before, the amount of urine for a period of four weeks, during which he was under observation, never exceeded 1,800 c.c. for twenty-four hours, and the specific gravity averaged 1.015, ranging from 1.005 (one record) to 1.031 (single specimen). The tabular record of the urine as well as the detailed history are given below. In the history it will be noted that in this patient, as in others, there are symptoms pointing suggestively to a cerebral origin for the diabetes insipidus. It was for the purpose of obtaining the cerebrospinal fluid for investigation by Dr. Dean D. Lewis, who was working on disease of the hypophysis, that the lumbar puncture was made. The result of the puncture suggests a certain relation between some cerebral condition and the polyuria. It also has a bearing on the theory of diabetes insipidus, which makes the disease largely dependent on the inability of the kidney to secrete a concentrated urine. A case like this would seem to show that under certain conditions the kidney of diabetes insipidus can, at least temporarily, pass a concentrated urine. The possible origin of the disease in this patient in a lesion of the brain, as in the hypophysis, and the very remarkable diminution in the amount of urine following lumbar puncture, which urine was of high specific gravity,

*Manuscript submitted for publication May 28, 1912.

with the bearing of this clinical experiment on questions of the pathogenesis of diabetes insipidus, are my reasons for making this brief report.

I append the history, with some minutiae that are perhaps unimportant but which may, in the light of later investigations, be seen to be of some significance. No attempt is made to classify this case as one of primary polyuria or of primary polydipsia, nor is any explanation of the phenomena volunteered, nor is there presented any review of the subject of the pathogenesis of diabetes insipidus. The theory of the inability of the kidney to secrete a concentrated urine — primary polyuria — is ably advocated by Erich Meyer.¹ The correctness of this view has been, in part, questioned by some, e. g., Finkelnburg,² and Forschbach and Weber.³ Meyer,⁴ however, still maintains that his notion is correct. The relation of the disease to lesions of the pars intermedia of the hypophysis has lately been discussed by E. Frank.⁵ Carbohydrate tolerance in connection with disease of the hypophysis has been considered by Goetsch, Cushing and Jacobson.⁶

CASE REPORT

Onset.—The patient was, at the time of onset, and had been for five years previously, a mail-carrier in the rural free delivery service, having to ride thirty miles daily over rough roads. There was some exposure to cold, but not excessive. Four years ago, in the spring, he first noticed frequent urination, both diurnal and nocturnal. This rapidly increased in frequency, until it became embarrassing. He would have to stop every half hour or even more frequently while on his route. Any attempt to suppress this tendency resulted in great misery. The quantities were large at each urination. There would be four or five nocturnal micturitions. The quantity was several quarts a day. His mouth and throat felt constantly parched, in spite of the great amounts of water drunk. The tongue was dry. Bulimia also developed in the spring.

These symptoms persisted all summer, and became more marked in the fall, when there were superadded others. There had been noticed during the summer some lessened physical endurance, but this became actual weakness. Lumbar pains became annoying. These usually began as a dull pain extending across the "small of the back." At times this radiated along the left gluteal region and down the left thigh following the course of the sciatic nerve; this radiation downward was very sharp and severe, much more so than the bilateral lumbar pain. These pains seemed to be precipitated by the jolting of the mail-cart. He would often get out and walk for relief. He had very little or no pain at night, and none after lying down for a little while.

1. Meyer, Erich: Ueber Diabetes Insipidus und andere Polyurien, *Deutsch. Arch. f. klin. Med.*, 1905, lxxviii; also *Fortschr. d. Deutsch. klin.*, 1910, ii, 271.

2. Finkelnburg: Ueber die Konzentrationsvermögen der Niere bei Diabetes insipidus nach organischen Hirnerkrankungen. *Deutsch. Arch. f. klin. med.*, 1910, c, 33.

3. Forschbach and Weber: Beobachtungen über die Harn- und Salzausscheidungen bei Diabetes insipidus, *Ztschr. f. klin. Med.*, 1911, lxxiii, 221.

4. Meyer, Erich: Bemerkungen zu der Arbeit von Forschbach und Weber, *Ztschr. f. klin. Med.*, 1912, lxxiv, 352.

5. Frank, E.: Ueber Beziehungen der Hypophyse zur Diabetes insipidus, *Berl. klin. Wochschr.*, 1912, xlix No. 9.

6. Goetsch, Cushing and Jacobson: Carbohydrate Tolerance and the Posterior Lobe of the Hypophysis Cerebri, *Bull. Johns Hopkins Hosp.*, 1911, xxii, No. 243.

Headaches, mostly occipital, though at times radiating to the frontal and ophthalmic regions, have annoyed him frequently for the last two years. These headaches were rarely severe. In the fall three years ago, after a long railroad journey, he had a severe headache which persisted twenty-four hours; he felt very weak, and could not sleep for pain. During this day he became very dizzy at any attempt to stand up, or even raise the head from the pillow; several times it "became black before his eyes." Once during the day, on attempting to rise, he fainted, and believes he was unconscious for three-quarters of an hour, during which time his wife tried to revive him with dashes of cold water. Ever since this day (he thinks) he has been much weaker. Often since then, and up to the present time, he has had transient attacks of vertigo, lasting a few seconds; he is sure he is never unconscious. These occur especially when he raises up suddenly after stooping over. There is a blackness before the eyes, and a sense as of everything being "faraway."

On comparatively slight exertion he has from this time up to the present noticed that the pulse is rapid and that he is conscious of the throbbing of the heart. Two months ago he had to stop three times while pushing a wheelbarrow 100 yards. He timed his pulse; it was 135. There were accompanying sensations of dyspnea and general nervousness. Mental emotion is also liable to bring on palpitation.

For over two years he has occasionally noticed transitory edema. Usually this would come on at night, would be noticed in the arm, and would disappear an hour or two after he arose, sometimes in the face, especially cheeks and eyelids; sometimes in the hands or feet. This has not increased lately in severity or frequency. This edema described by the patient was not seen while he was in the hospital.

For the last year or two he has had mild and variable paresthetic sensations, especially noticed when he awakes in the night, such as a sense of numbness involving the limbs or even whole body. Oftener a localized numbness involving some special, but variable, area on the fingers or toes. Thus once there was an involvement of the distal part of the left index and middle fingers, lasting perhaps half an hour. Very often this takes the form of a prickling, as with needles and pins. He has noticed these paresthesias perhaps six times the last month.

The skin has been abnormally dry for about four years; also cold. Even in hot weather he sweats but little. Pruritus was marked two years ago; as also an oily condition of the skin. The last year there have occasionally appeared on the instep of the foot very minute (miliary) vesicles, filled with clear serum. There is intense itching. He scratches them until they bleed.

There are few gastro-intestinal disturbances, though he says the abdomen is at times distended with gas in the bowels.

For over thirty years he has found it impossible to read long without glasses. Even with lenses he often has to stop after reading five or ten minutes, on account of blurring of vision and pain in the eyeballs. But he has never been fitted by an oculist. No amblyopia, diplopia or scotomata.

For many years he thought he "had no nerves;" the last four years he has frequently felt very nervous; these attacks of weakness, nervousness and even trembling come on with physical exertion, or even slight mental excitement.

Attacks resembling *petit mal* occur. He and his family have noticed the last year that while reading or talking he will occasionally stop abruptly for a few seconds and cease all activities. This lapse will terminate abruptly. These attacks have nothing in common with the attacks of vertigo.

He has been a light sleeper all his life; the last four years this condition has been decidedly aggravated; apparently, this is due largely to the necessity of awakening for urination. The patient was worried much lately because he thinks his mentality has been affected.

After the development of the symptoms four years ago, the conditions became gradually more marked. Three years ago a physician was consulted, especially

on account of the lumbar pains, which finally rendered work almost impossible. There was polyuria, with low specific gravity; no sugar; no albumin. Treatment was of no avail.

The patient was very sick for ten days following vaccination at age of 15. When 7 or 8 years of age the patient had to stop school on account of some paralysis of the legs. He remembers having been carried around for weeks. He was well otherwise. He used crutches later. There was no pain. (Poliomyelitic?)

The patient had "yellow jaundice" when a child, bronchopneumonia at 9, scarlatina at 10, otorrhea once (cannot remember which ear); earache often. At 23 he had a severe diarrhea with hemorrhage—sick in bed four or five days. Eleven years ago he had "walking typhoid"—fever 104 F. Some headache and diarrhea. Seventeen years ago he had extensive furunculosis.

When a boy (up to the age of 17 or 18) he had sick headaches frequently (about once a month), frontal and temporal, and very violent in one eye (he cannot remember which). He went to bed with these.

At 17 suffered a violent head trauma (thrown out of wagon on head); was unconscious a short time; headache a few days.

The patient was a carpenter for many years. For the five years preceding the onset of these attacks he was a rural mail-carrier.

Formerly he used beer and a little whiskey, very moderately; latterly no alcohol. He used coffee excessively for many years (five to eight cups a day). He quit after the onset of the present illness and the symptoms ameliorated for a month or two (first summer).

The patient's mother died of puerperal fever, his father at advanced age of a slowly advancing paralysis following a "stroke" ten years before.

He was married at 21. His wife has had four healthy children and two miscarriages—her third and fourth pregnancies, and early in each pregnancy. He has noticed no failure of sexual power. He denies venereal disease.

Present Status.—Polyuria marked—seven to ten quarts a day; polydipsia, with excessive thirst and dryness of mouth; appetite voracious; weakness marked. Two blocks of fast walking would fatigue him, and also bring on dyspnea and palpitation. Headache—occipital—frequent, but never severe. Transient vertigo and occasional attacks resembling petit mal; general nervousness; paresthesias; dry skin; lumbar pains only if he over-exerts.

He has gained fifteen pounds the last four years and weighs now 154 pounds. There is no disturbance of taste, smell or audition (?), no paralyses, no dysuria, no cough, no jaundice, no sore throat.

Physical Examination.—He was a moderately thin, healthy-looking man, who, while saying he felt rather weak, yet walked into the hospital. He impressed one as neurotic, dwelling on and magnifying trifling symptoms, but not acting as an hysterical patient. And no hysterical somatic stigmata were found on any examination. His color was good, the skin a little tanned as from exposure to the weather. There was no wasting of the subcutaneous fat. No rashes, ecchymotic spots or suspicious (lucic) scars were found. He was not icteric. The skin was dry. There was no adenopathy.

The reflexes were normal—pharyngeal, epigastric, hypogastric, cutaneous, cremasteric, patellar, Achilles. There was no Babinski; no ankle clonus; no Romberg. Sensory disturbances could not be made out.

The heart was not enlarged on percussion. Its apex impulse was inside the mamillary line; its tones were pure; its beat rhythmic. The peripheral vessels were not thickened or tortuous. The radial systolic pressure was 123 mm. Hg (Riva-Rocci, modified by Stanton).

The examination of the scalp and cranium gave normal findings, as did that of the ears, nose and mouth. Hearing was perhaps a little dull. The eyes were examined with especial care (Dr. W. H. Wilder), and found normal except for a marked arcus senilis in each eye. The reactions of the iris to light and in

accommodation and consensually were active. No exophthalmos, nystagmus, ptosis or paresis of the external muscles could be made out. Ophthalmoscopic examination and testing of the fields of vision revealed normal conditions. Some of the optic nerve fibers were medullated. No scotomata. An *x*-ray examination of the cranium showed a sella turcica that appeared smaller than normal. In other respects the radiograph was negative.

There was no enlargement of the thyroid gland and no dulness to suggest a sub-sterially enlarged thyroid or thymus gland. The chest was well-formed, with normal pulmonary resonance and free excursion on respiration. Breath sounds were normal; no râles.

The abdominal examination revealed nothing abnormal. The spleen and kidneys were not palpable, the liver not enlarged, the stomach apparently in normal position and of normal size. The genitalia were normal. Rectal examination was negative.

The blood count was 5,088,000 red corpuscles; 6,450 whites; hemoglobin, 84 per cent. The varieties of white corpuscles were in normal proportions.

February 17. Wassermann (Dr. Nicoll) negative.

February 18. Patient states that he is positive he is passing more urine since entering the hospital; attributes this to the fact that at home he rests a great deal in a spring-chair inclined at an angle of 145 degrees. He believes the kidneys are more congested by his use of the hospital chairs (upright).

February 19, 11 a. m. Lumbar puncture. Less than 5 c.c. of cerebrospinal fluid removed; perfectly clear; came out under normal or somewhat reduced pressure. Within five minutes after the withdrawal of the fluid he complained of a headache and pain in the back of the neck. It rapidly radiated upward to the occiput and downward along the spine, growing more intense, so that within half an hour it was the most violent headache he had ever had. The occipital, temporal, frontal and vertical regions of the scalp were also involved. The pains also radiated down the arms to the elbow. The slightest movement of the body, neck or even fingers, resulted in exacerbations of the headache. The neck was somewhat rigid (seemingly held so voluntarily to avoid pain). There was no pain on pressure over nerve trunks. Kernig sign somewhat positive. There was also a feeling of soreness deep in the lower substernal and epigastric regions. No nausea.

February 20, p. m. (thirty-six hours). The head and backache somewhat easier, provided patient lies perfectly quiet. Any slight motion of the trunk, neck, head or limbs is followed by intense exacerbation of the pain. The patient "suffered agony" yesterday and this morning. The Kernig has disappeared. There has been some nausea and vomiting.

February 25 (notes on days February 20-25). The headaches have gradually cleared up during the last two or three days. Patient has noticed a great change in physical and mental condition. Since the lumbar puncture his skin has been moist and warm (verified often by Dr. Kirk, the intern) in contrast with the dry condition of the last two or three years. Patient feels relieved mentally; the depression is gone and he feels very much encouraged. The soreness of the muscles and in the neck incident to the puncture has worn off. Has never passed so little urine in four years.

The patient left for home and re-entered the hospital after being absent for nine days. He reports that the headaches have gradually worn off, so that at present they are not so severe. The thirst has been less marked; not more than two quarts of liquid a day, being taken. The urine has been noticeably small in amount, one day about three pints. Also the frequency of micturition is much less. Since the lumbar puncture, he has often gone from six to twelve hours without urinating. He states definitely that up to the time of the puncture he for four years urinated at least every two hours—often every hour, or more frequently. Since the puncture the appetite has been decidedly less. He believes his appetite is now about that of an average man. At times he feels rather

nauseated on attempting to eat certain foods, as eggs. The skin has been decidedly more moist ever since the puncture. He has had no more of the attacks resembling petit mal. Has had slight vertigo several times, on suddenly raising the head after lying down. The tingling in the arms has come on a few times, lasting five or ten minutes each time. He believes the weakness is more marked than before the puncture. Sleeps better. The lumbar pains have been experienced a few times, as before the puncture. Physical examination the same as before: the systolic radial blood-pressure is 122. Skin normally warm and moist. Ophthalmoscopic examination again shows normal retina.

Sugar toleration was tested with the following result:

March 8. 100 g. glucose this p. m. March 9. no glycosuria.

March 9. 200 g. glucose. March 10. no glycosuria.

March 10. 300 g. glucose. No glycosuria.

An imperfect chlorid toleration test was made, the results of which are not given.

URINARY CHART

Dates	Amount	Specific Gravity	Remarks*
.....	c.c.	(Approx.)
February, 1912			
14	6,750	1001
	(18 hrs.)		
15	8,920	"
16	10,180	"
17	7,740	"
18	11,320	"
19	11,380	"
20	10,710	1000.5	11 a. m.: lumbar puncture
21	4,220	1001
22	660	1017
23	1,490	1014
24	1,410	1014
March	Single		
6	admission specimen	1031
7	1,280	1018
8	905	1016
9	1,310	1015	100 g. glucose yesterday
10	1,520	1015	200 g. glucose yesterday
11	1,340	1007	300 g. glucose yesterday
12	1,440	1010
13	1,560	1010
14	1,800	1010	Pituitrin started; all 2 doses (15 m. subcut., and 2 m. intravenously) were given on the 14th and 15th days.
15	1,460	1050
16	1,000	1024
17	1,720	1014
18	905	1023	M. iii pituitrin given intravenously twice.
19	980	1015	M. vii given twice intravenously to-day.
20	860	1020	None given since; KI started, gr. x. t. i. d.
21	1,280	1013
22	1,020	1014
23	620 (?)	1027
24	1,160	1006
25	920	1012

*At no time, even after the glucose, was sugar found in the urine. There was never albumin. No casts or other pathologic microscopic structures were found. Diacetic acid and acetone were tested for often, but were never detected. The urine was always acid. After the lumbar puncture it was of darker color than before and at times was a little turbid.

March 14. Two doses of 15 m. pituitrin (P. D. and Co.) given hypodermatically.

March 15. M. ii given intravenously.

March 18. M. iii given intravenously; blood-pressure ten minutes later, 133. Repeated in evening.

March 19. M. vii given intravenously twice to-day.

Blood-pressure 124 before; 155 afterward (five minute).

March 25. Present Status: (a) No thirst; (b) no polyuria; (c) no attack resembling petit mal; no nausea; no vomiting; (d) irregular headaches (severe at times), some lumbar pains, some left sciatic pain. Eyesight just about same as before (occasional visual disturbances, as formerly). The patient at this time left for home. No word has since come from him.⁷

122 South Michigan Avenue.

7. As this goes to press I am told by a neighboring physician who is familiar with the case that the old symptoms have been returning.

THE COBRA VENOM HEMOLYSIS TEST IN SYPHILIS, WITH REPORT OF ONE HUNDRED AND THIRTY REACTIONS *

WILLARD J. STONE, M.D., AND RICHARD SCHOTTSTAEDT, M.D.
TOLEDO, O.

HISTORICAL

Much of the early work on cobra venom hemolysis was done by Calmette,¹ Stephens,^{2, 3} Myers,^{2, 4} Mitchell and Flexner,⁵ Flexner and Noguchi,⁶ Kyes,^{8, 9} Sachs,^{9, 10} Abderhalden and LeCount,¹¹ and Goebel.¹² Additional papers by Noguchi,⁷ von Dungern and Coca,¹³ Bang¹⁴ and Weil¹⁵ have, within the past five years, created new interest in the subject. From the work of Kyes it has been shown that the incomplete hemolysin present in native cobra venom (amboceptor, as first suggested by Flexner and Noguchi) is activated, in the absence of serum, by complementing substances (lecithin) present in the red cells to form the complete hemolysin, called by him "cobra-lecithid."

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*Read at the meeting of American Association of Pathologists and Bacteriologists, Philadelphia, April 6, 1912.

1. Calmette: *Ann. de l'Inst. Pasteur*, 1892, vi; *Compt. rend. Soc. de biol.*, 1894; *Compt. rend. Acad. d. sc.*, 1902, cxxxiv, 1446.

2. Stephens and Myers: *Brit. Med. Jour.*, Mar. 5, 1898; *Jour. Path. and Bacteriol.*, 1898, v, 279.

3. Stephens: *Jour. Path. and Bacteriol.*, 1900, vi, 273.

4. Myers: *Jour. Path. and Bacteriol.*, 1900, vi, 415; *Trans. Path. Soc., London*, Feb. 6, 1900.

5. Mitchell and Flexner: *Nat. Acad. Sc.*, 1901.

6. Flexner and Noguchi: *Jour. Exper. Med.*, 1902, vi, 277; *Univ. Penn. Med. Bull.*, 1902, xv, 345.

7. Nóguchi: *Jour. Exper. Med.*, 1907, ix, 436; *Serum Diagnosis of Syphilis*, Lippincott, Phila., 1911; *Snake Venoms*, Chap. xvi, Carnegie Institution, Washington, 1909.

8. Kyes: *Berl. klin. Wehnschr.*, 1902, xxxix, 886; *ibid.*, 1903, xlii, 21; *ibid.*, 1903, xlii, 956; *Biochem. Ztschr.*, 1907, iv, 109; *Jour. Infect. Dis.*, 1910, vii, 181.

9. Kyes and Sachs: *Berl. klin. Wehnschr.*, 1903, xlii, 21, 57, 82.

10. Sachs: *Centralbl. f. Bact.*, 1903, xxxiv, 686; *Biochem. Centralbl.*, 1906, v, 257; *München. med. Wehnschr.*, 1908, lv, No. 9.

11. Abderhalden and LeCount: *Ztschr. f. exper. Path. u. Therap.*, 1905, ii, 199.

12. Goebel: *Compt. rend. Soc. de biol.*, 1905, lviii, 420.

13. Von Dungern and Coca: *München. med. Wehnschr.*, 1907, iv, 2317; *ibid.*, 1908, lv, 105; *Biochem. Ztschr.*, 1908, xii, 407; *Jour. Infect. Dis.*, 1912, x, 57.

14. Bang: *Biochem. Ztschr.*, 1908, xi, 521.

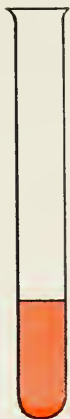
15. Weil: *Proc. Soc. Exper. Biol. and Med.*, 1909, vi, 49; *ibid.*, 1909, vii, 2; *Jour. Infect. Dis.*, 1909, vi, 688.

COBRA VENOM REACTIONS IN SYPHILIS

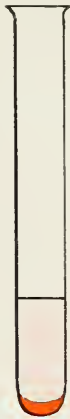
Dilution
1-10,000



Dilution
1-15,000



Dilution
1-20,000

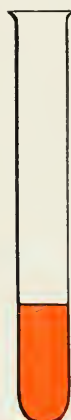


Dilution
1-30,000



Marked Positive

1-10,000



1-15,000



1-20,000



1-30,000



Positive

1-10,000



1-15,000



1-20,000



1-30,000



Negative

According to Hober¹⁶ lecithin, with a small amount of cholesterol, is said to form 33 per cent. of the solid ingredients of red cells. Sachs has suggested that the hemolytic resistance of red cells, from different individuals of the same species, varied according to the amount of lecithin in the cells. Kyes, on the other hand, while substantiating in the main the results obtained by Sachs, believes that, since all erythrocytes contain sufficient lecithin to activate cobra venom, the varying susceptibility of red cells to the venom depends rather on the availability of the intracellular lecithin for the reaction. That is, whether the lecithin in its combination with the cell structure, is available in a free state.

Any factor, therefore, which modifies the availability of the cell lecithin may modify the susceptibility of the cells for hemolysis with cobra venom. Thus, the erythrocytes of sheep, ox, or goat, in physiological salt solution, which are never susceptible to cobra venom irrespective of the strength of solution employed, become highly susceptible to venom when the cells are suspended in physiological sugar solution. Also, certain lipid substances, such as the fatty acids, neutral fats and soaps of the fatty acids, possess certain powers, probably through modification of the cells, to render more available the intracellular lecithin for the formation of the complete hemolysin. Since these substances act through modification of the cells, indirectly affecting the availability of the contained lecithin, they are considered to be indirect activating agents. Chloroform, ether and bile salts fall into this class.

In susceptible cells, on the other hand, the union of cobra venom and lecithin occurs directly with the formation of the complete hemolysin, designated by Kyes cobra-lecithid, due to a splitting of the fatty acid radical from the lecithin. Lüdecke,¹⁷ von Dungern and Coca¹⁸ and Manwaring¹⁸ have contended, however, that this product was a venom-free lecithin derivative and not a lecithid. They have preferred to call the active principle "cobralecithinase" and the hemolytic end-product, "mono-fatty-acid lecithin" or "desoleo-lecithin." Von Dungern and Coca do not believe that lecithin acts as a complement in the reaction.

In the study, however, of the behavior of cobra venom solutions and red cells, definite quantitative relations have been shown to exist between the strengths of solutions and the amounts of lecithin contained in the cells. As mentioned by Kyes, these results "are comparable to those given by Morgenroth and Sachs¹⁹ for complement and amboceptor in hemolytic sera; viz., that within certain limits, the larger the amount of

16. Hober (Quoted by Schwartz): "Chemie der Zelle." Ed. 2, 1906.

17. Lüdecke: Inaugural Dissertation, München, 1905. (Quoted by Schwartz, N. Y. Med. Jour., 1912, xcv, 23.)

18. Manwaring: Johns Hopkins Hosp. Bull., September, 1910; Ztschr. f. Immunitätsf., 1910, vi, 513.

19. Morgenroth and Sachs: Berl. klin. Wchnschr., 1902, xxxix, 817.

venom, the smaller the amount of lecithin required to effect hemolysis: and vice versa, the larger the amount of lecithin the smaller the amount of venom required." On the other hand, with a fixed amount of lecithin, an increase in the amount of venom beyond the usual requirements for hemolysis inhibits the lysis, since the quantitative relations between the substances have been disturbed, a condition analogous to the Neisser-

TABLE 1.—SPECIFIC REACTIONS IN LUECTICS AND CONTROLS

Serial Number	Stage	Duration, Years	Wassermann	Noguchi Butyric Acid Test*	Cobra Venom Test
2.	Tertiary, active	2	+	..	+
3.	Primary	1/8	+	..	+
4.	Congenital, active	..	+	..	+
11.	Secondary, active	5/12	+	..	+
14.	Normal	..	—	—	—
15.	Normal	..	—	..	—
18.	Psoriasis	..	—	..	—
20.	Clin. cured	5	—	..	—
40.	Secondary, active	1/2	+	..	+
46.	Tertiary, active	5	—	..	+
48.	Tabes, dorsalis	3	+	..	+
50.	Normal	..	—	..	—
53.	Tertiary, active	5	+	..	+
62.	Tertiary, latent	†	..	+	+
63.	Normal	—	—
64.	Gen. paralysis	‡	..	+	+
65.	Tertiary, latent	4	+	+	+
69.	Gen. paralysis	‡	..	+	+
74.	Gen. paralysis	7	..	+	+
80.	Tertiary, active	16	..	+	+
81.	Gen. paralysis	12-14	+	+ in cerebro-spinal fluid.	—
82.	Gen. paralysis	‡	+	+ in cerebro-spinal fluid.	+
83.	Cerebral syphilis	‡	+ in cerebro-spinal fluid. Neg. in blood.	+ in cerebro-spinal fluid.	—
84.	Progr. bulbar palsy	— in cerebro-spinal fluid.	—
86.	Chr. pulm. tubercu.	—	—

*Blood-serum was used in making the butyric-acid test except in cases so designated.

† Lues denied. ‡ Unknown.

Wechsberg phenomenon, in which an excess of amboceptor inhibits the action of a minimal amount of complement.

VENOM HEMOLYSIS IN SYPHILIS

The considerations above described, while interesting from a theoretic standpoint, did not produce results of a practical nature until the publications of Weil, who found in testing the hemolytic powers of cobra

venom, with cells derived from different types of disease, that the red cells of luetic individuals offered increased resistance to hemolysis. It was demonstrated that normal erythrocytes, and erythrocytes derived from individuals with diseases other than syphilis, would undergo complete hemolysis in dilutions as high as 1 in 30,000 to 1 in 40,000; while luetic red cells showed little or no hemolysis in dilutions varying from 1 in 15,000 to 1 in 30,000. Weil's conclusions based on the reactions obtained in 191 cases showed that this characteristic was especially true of advanced syphilis.

One of three explanations is available for the phenomenon: (1) Either the quantity of red cell lecithin is actually diminished in syphilis, after the primary stage, as a reactive phenomenon to the luetic toxin; or (2) the toxin so affects the stromata-holding lecithin as to render less of it available in a free state for the formation of the hemolysin, "cobra-lecithid" (Kyes) or "monofatty-acid lecithin" (von Dungern, Coca, Manwaring); or (3) a dissociation has taken place between lecithin and cholesterol in the red cells with inhibition of hemolysis by the latter substance.

Weil has called attention to the fact that syphilis attacks the lipid constituents of body cells, since the amount of lecithin which can be extracted in syphilis is less than can be obtained from normal tissues. In explanation of the increased resistance of luetic red cells to cobra venom hemolysis, he has suggested that possibly the luetic toxin attacks the same cellular constituents as cobra venom in much the same way that the hypodermic injection of phenyl-hydrazine produces an increased red cell resistance to all hemolytic agents including cobra venom. Such a result is probably a reactive phenomenon of tolerance, for Weil has shown that repeated injections of such an hemolytic agent as saponin leads in rabbits to the production of red cells which show marked resistance to saponin hemolysis but to no other hemolytic agents. The first generations of cells were found to be hypersusceptible to the action of saponin but subsequent generations had acquired tolerance to it.

Such a phenomenon apparently occurs in the reaction of luetic red cells to cobra venom. For about five or six weeks after the primary lesion the red cells are hypersusceptible to cobra venom hemolysis in all dilutions. Subsequent generations of red cells after six or eight weeks (about the time of secondary manifestations) acquire tolerance and become resistant to this hemolytic agent. The phenomenon of acquired resistance to saponin hemolysis is different, however, from the reaction of luetic cells with cobra venom. In lues, the reaction occurs in response to the luetic virus, with subsequent increased hemolytic resistance, to a toxin of dissimilar origin. The acquired tolerance to saponin manifests itself against saponin alone. The increased resistance of luetic cells to the

hemolysin of cobra venom is apparently the first instance of specific alteration of diseased body cells to an hemolytic agent.

Whatever may be the ultimate explanation, it is certain that the reaction is characteristic of certain stages of syphilis, for in no other condition or disease has the same degree of resistance been encountered.

THE COBRA VENOM TEST AND TECHNIC

We are indebted to Dr. Weil for two samples of cobra venom. One was obtained from Calmette of Lille and the other from Coca. The two specimens, when tested in various dilutions with normal and specific bloods, were found to possess equal hemolyzing powers. It is probable that the strength of the dried venom does not vary, although preliminary titration against red cells of normal and luetic individuals will determine the hemolyzing strength of any sample.

The stock solution consists of

Dried cobra venom	0.005	=1-2000 dilution
0.9 per cent. solution NaCl	10.0	

This stock solution if stored in the ice chest, keeps for at least one week.²⁰ From this stock solution the following dilutions are made, using separate clean pipettes for each dilution. All subdilutions are kept in the ice chest:

SUB-DILUTIONS

Solution "A"—1:10,000=1 c.c. stock sol. plus 4 c.c. 0.9 per cent. NaCl sol.

Solution "B"—1:15,000=2 c.c. sol. "A" plus 1 c.c. 0.9 per cent. NaCl sol.

Solution "C"—1:20,000=1 c.c. sol. "A" plus 1 c.c. 0.9 per cent. NaCl sol.

Solution "D"—1:30,000=1 c.c. sol. "B" plus 1 c.c. 0.9 per cent. NaCl sol.

The blood is drawn from one of the veins at the bend of the elbow with a 5 c.c. glass Luer syringe to which is attached an ordinary antitoxin needle with flexible rubber connection. The syringe should contain about 2 c.c. of a 2 per cent. solution of sodium citrate (free from air bubbles). The exact amount of citrate solution is unimportant. The needle is passed through the flame several times. A piece of rubber tubing is tied above the elbow tight enough to constrict the superficial veins, the patient being in the prone position. The arm is cleansed with alcohol, and the needle inserted into the vein. The blood flows into the citrate solution in the syringe and, from its own pressure, gradually pushes the piston upward. When about 2 c.c. of blood has flowed into the syringe, the rubber constriction is loosened. Pressure with a compress of cotton is made over the point of the needle to prevent a hematoma, and the needle quickly withdrawn. The blood solution is then expelled into a 15 c.c. graduated centrifuge tube, and placed in the ice-box until ready for use (if necessary for 24 hours).

20. a. If the stock solution (after a suggestion by Schwartz) is divided into ten parts of 1 c.c. each and the tubes placed in a wide-mouthed, well-corked vacuum bottle containing salt and ice and kept frozen in the ice-chest, the strength of the venom solution remains unchanged. This procedure prevents waste of the venom solution. Since 1 c.c. of the stock solution is sufficient for two complete test series of subdilutions, 1 gm. of cobra-venom is sufficient for 4,000 tests. The wide-mouthed vacuum bottle may be obtained from E. Machlett & Son, 143-147 East Twenty-Third Street, New York. b. If the dried venom crystals are pulverized in a mortar with benzene (after a suggestion by Weil) and the benzene evaporated, a homogeneous powder results which is easier to weigh and to dissolve. c. We have modified the technic suggested by Weil for purposes of simplification.

One should avoid shaking the cell suspension. When ready for use any clots which have formed on the bottom of the tube are first fished out with a platinum wire and the supernatant citrate solution removed with a capillary pipette. The tube is then filled with a 0.9 per cent. solution NaCl, and centrifuged at moderate speed until the solution is clear (for 10 minutes). The salt solution is pipetted off and the process repeated three times more to remove all serum which, at least in some instances, inhibits hemolysis. Of the washed cells 0.6 c.c. should remain in the tube and 0.9 per cent. NaCl sol. added to 15 c.c. (a 4 per cent. suspension). In order to secure the same density of packed cells in the tube, it is necessary to centrifuge for a definite number of minutes. It is important to have the red cell suspension accurately made in order to secure uniformity in a series of tests. When ready for use, the red-cell suspension is gently shaken, once or twice, to secure even distribution of cells. One c.c. cell suspension is then added to 1 c.c. of venom dilutions; 1:10,000; 1:15,000; 1:20,000; 1:30,000. The tubes are covered with tin foil and placed in the incubator for one hour at 37 C. The tubes are then gently shaken and placed in the ice-box over night when they are again gently shaken, and the readings taken one hour later. The 1:10,000 tube is used as a control on the dilutions of venom, since practically all human bloods will hemolyze in dilutions of 1 to 10,000. If hemolysis should occur in higher dilutions and not in the 1 to 10,000 tube, pointing to discrepancy in technic, fresh solutions should be made and the test repeated. The readings are marked as follows:

- ++ = Complete hemolysis.
- + = Incomplete or partial hemolysis.
- = Hemolysis absent.

Practically all bloods will hemolyze in dilution 1:10,000 and all normal bloods in dilution 1:15,000, 1:20,000 and 1:30,000. If no hemolysis occurs in 1:15,000, in 1:20,000 and 1:30,000 tubes the result is strongly positive; if complete hemolysis occurs in dilutions 1:10,000 and 1:15,000, but none in 1:20,000 and 1:30,000 the result is positive. If complete, or almost complete, hemolysis occurs in all dilutions including 1:20,000 and 1:30,000, the result is negative (see plate). If complete hemolysis occurs in all dilutions within one hour after their removal from the incubator, the cells are regarded as hypersusceptible to cobra venom. Hypersusceptibility occurs as a rule in syphilis until the fifth or sixth week after the primary lesion, and in tuberculosis when in an active stage.

REMARKS ON THE TECHNIC

It seems certain that sodium citrate plays an essential part in the reaction, for we have been unable to obtain satisfactory results without it. In fact, defibrinated blood hemolyzes in the dilutions concerned in the test within twenty-four hours regardless of the presence or absence of syphilis. In addition, if citrate solution is added to defibrinated blood, the hemolysis is retarded in the case of luetic blood and increased in tuberculous blood in a manner similar to that which occurs when blood is drawn into the citrate solution. The presence of fibrinogen or fibrin evidently has nothing to do with the reaction, and although lecithin is present in the blood plasma, it is probably not present as such in a free or available state. An appreciable amount of serum does not apparently retard the hemolysis.

TABLE 2.—COBRA VENOM HEMOLYSIS IN LUES AS AFFECTED BY TREATMENT

Stage	Years Duration	Treatment	Cobra Venom Dilutions				Result
			10,000	15,000	20,000	30,000	
Primary	1/8	Hg. and Iod. 2 weeks. Salvarsan int. muse. 4 weeks ago.	+	—	—	—	Mkd. pos.
Second, active	5/12	Hg. and Iod. 4 mo. Salvarsan int. muse. 3½ mo. ago.	++	++	+	—	Positive.
Second, latent	2/3+	Hg. and Iod. 7½ mo. Salvarsan int. muse. 7 mo. ago.	++	++	+	—	Positive.
Clin. cured.	10/12	Hg. and Iod. 8 mo. Salvarsan 0.4 G. int. ven. 3 weeks ago; int. muse. 8½ mo. ago.	++	++	++	+	Negative.
Clin. cured.	1	Hg. and Iod. 8 mo. Salvarsan 0.4 G. int. ven. 3 mo. ago. Int. muse. 10½ mo. ago.	++	++	++	++	Negative.
Congenital, act.	33	Hg. and Iod. 4 mo.	+	—	—	—	Mkd. Pos.
Clin. cured	..	Hg. and Iod. 15 mo. Salvarsan 0.2 gm. int. ven. 2 mo. ago.	++	++	++	+	Negative.
Second, active	1/3	Hg. and Iod. 3 mo.	++	+	—	—	Positive.
Clin. cured	11/12	Hg. and Iod. 6 mo. Salvarsan 0.5 gm. int. ven. 6 weeks ago.	++	++	++	+	Negative.
Second, active	1/2	Hg. and Iod. 4 mo.	++	+	—	—	Positive.
Clin. cured	3/4	Hg. and Iod. 8 mo. Salvarsan 0.4 gm. int. ven. 1 mo. ago.	++	++	++	++	Negative.
Second, latent	2—	Hg. and Iod. irreg. 1 year.	++	+	—	—	Positive.
Second, latent	2	Hg. and Iod. irreg. 1 year. Sal- varsan 0.4 gm. int. ven. 3½ mo. ago.	++	+	—	—	Positive.
Second, active	10/12	Hg. and Iod. 8 mo.	++	++	+	—	Positive.
Second, latent	1	Hg. and Iod. 8 mo. Salvarsan 0.5 gm. int. ven. 10 weeks ago.	++	++	+	—	Positive.
Clin. cured	1 1/6	Hg. and Iod. 8 mo. Salvarsan 0.5 gm. int. ven. 4½ mo.	++	++	++	++	Negative.
Tertiary, active	16	None	++	++	+	—	Positive.
Tertiary, latent	16 1/2	Hg. and Iod. 4 mo.	++	++	+	—	Positive.
Primary	6*	None	++	++	+	+	Suspici's.
Second, active	13*	Hg. and Iod. 1 mo. Salvarsan 0.4 gm. int. ven. 7 weeks ago.	++	++	+	—	Positive.
Second, latent	1/3	Hg. and Iod. 2 mo. Salvarsan int. ven. 3 mo. ago.	++	+	—	—	Positive.
Second, latent	1 3/4	H. and Iod. irreg. Salvarsan int. muse. 9 mo. ago.	++	++	—	—	Positive.
Clin. cured	2	Hg. and Iod. irreg. Salvarsan int. muse. 9 mo. ago. 0.4 gm. salvar- san int. ven. 6 weeks ago.	++	++	++	++	Negative.
Tertiary, active	2 1/2	Hg. and Iod. 4 mo.	++	—	—	—	Mkd. Pos.
Tertiary, latent	2 2/3	Hg. and Iod. 4 mo. Salvarsan 0.4 gm. int. ven. 6 weeks ago.	++	++	+	+	Suspici's.
Tertiary, latent	2 2/3+	Hg. and Iod. 4 mo. Salvarsan 0.4 int. ven. 2 mo. ago.	++	+	+	—	Positive.
Second, latent	1	Hg. and Iod. irreg.	++	++	—	—	Positive.
Clin. cured	1 1/6	Hg. and Iod. irreg. Salvarsan 0.4 gm. int. ven. 1 mo. ago.	++	++	++	++	Negative.

*Weeks.

CLINICAL DIAGNOSIS

In the earlier part of our work the complement fixation method of Wassermann was used as a control, in a limited number of cases. The readings and results were practically parallel. The list of tests with normal blood and bloods from individuals with no clinical evidences of lues, but with other diseases, shows a negative result in all except in one patient with morbilliform erythema. This brings us to the point of interpretation of results. It may be taken for granted that each clinician, according to his experience, makes the mental reservation when obtaining the essential points in the history of a patient, whether such a patient, before further examination, is to be classed as (1) surely luetic, (2) probably luetic, or (3) probably non-luetic.

In the diagnosis of duodenal ulcer, for example, a careful history is often of more aid than the clinical findings, while in the clinical diagnosis of latent syphilis, a careful history dealing with the sequelæ of each year subsequent to the date of the supposed infection is most essential. Patients are so often told after a cursory examination that an earlier small erosion had no significance. Likewise because of a neisserian infection the possibility of a coexistent hunterian chancre is many times forgotten. Such incidents are not rare, nor are extragenital primaries uncommon. On the other hand, little importance can be attached to the patients' statements as to the *absence* of sequelæ following a suspected lesion. Many of the manifestations of the disease may have been present, but their absence from the patient's point of view does not exclude syphilis.

The longer one works with specific tests the more impressed does one become with the varied manifestations and effects of the disease. In fact, as Cabot has stated, "anyone may have syphilis and be innocent of it." The remote effects of the disease, in whatever form, are so numerous and varied as to keep every clinician on his guard. This is particularly true of the congenital forms. In fact, the symptomatology of congenital and latent lues is as varied from a clinical standpoint as the colors of Joseph's coat. A considerable portion of so-called mentally deficient children suffer from congenital syphilis (36 per cent. of forty-nine cases, Corson-White and Ludlum²¹). Also a fairly large proportion of apoplectic seizures in comparatively young individuals (under 40), if chronic nephritis and valvular disease can be excluded, are on a luetic basis.

Likewise in many cases of so-called spontaneous or idiopathic epilepsy developing after the age of 15, lues plays an important rôle. Such an instance was found in Case 80 of this series. The epileptiform seizures developed at the age of 21, six years after an ignored and forgotten

21. Corson-White and Ludlum: Jour. Nerv. and Ment. Dis., 1910, xxxvii, 721.

primary, coincidental with neisserian urethritis. These attacks had recurred at intervals of one month for ten years. The cobra venom test was positive on two occasions and the blood serum contained a markedly increased globulin precipitate, using the method described by Noguchi²² for cerebrospinal fluid. It was not considered advisable to do lumbar puncture on the patient. Since the inauguration of antisyphilitic treatment four months ago, no attacks have occurred.

We have on numerous occasions found it interesting to test the blood serum for increased globulin, instead of the cerebrospinal fluid, according to the method described by Noguchi for the latter.²² It does not appear necessary to use the more complicated method described by him for blood serum, since the globulin increase in syphilis, if present at all, seems to affect as distinctly the blood serum as the cerebrospinal fluid, and the simpler test often suffices. It is probably better, however, when possible, to test, in addition, the cerebrospinal fluid for increased globulin, by the butyric acid method of Noguchi, in any suspected form of cerebrospinal syphilis. If cerebrospinal fluid is used, the test is frequently positive in cerebral syphilis and general paralysis, although it may also be positive in tuberculous meningitis and acute meningitis from other causes. The test is negative in the psychoses, in cerebral arteriosclerosis, in brain tumor other than gumma, and in non-inflammatory meningeal irritation.

In the experience of Corson-White and Ludlum, "the globulin increase constantly accompanies primary, secondary and tertiary syphilis, tabes and paresis. In paresis the test is strongly positive in the blood and cerebrospinal fluid, while in cerebrospinal lues and tabes, increased globulin is a much more constant symptom than the complement fixation test. The non-specificity of the globulin test detracts from its diagnostic importance but not from its corroborative value, for the absence of the butyric acid reaction is more proof of the absence of syphilis than the absence of the Wassermann reaction. In tertiary syphilis of the nervous system the butyric acid test was positive in 94 per cent., the Wassermann in 67 per cent., while the cobra venom test was positive in only 22 per cent."

Corson-White²³ has recently stated that in syphilis of the central nervous system, general paralysis and tabes (598 cases) the Wassermann test was positive in 82.5 per cent., the cobra test in 33.3 per cent.

22. To 1 c.c. of a 10 per cent. solution of pure butyric acid in physiological salt solution, in a test tube, 0.2 c.c. of blood serum or cerebrospinal fluid is added. The mixture is heated to boiling, 0.2 c.c. of normal sodium hydrate is added and the mixture again boiled. In the presence of increased globulin a definite flocculent precipitate occurs, either immediately or within an hour or two. This precipitate must be differentiated from a faint cloudiness which normal sera may give, but it requires only slight experience to differentiate between positive and negative reactions.

23. Corson-White: Personal Communication.

THE INTERPRETATION OF HEMOLYSIS TESTS

It has proved instructive from many points of view to attempt to correlate the clinical history before an hemolysis test with the subsequent findings. In fact, in satisfying one's self as to the value of any method, it is essential to know with some degree of accuracy what is expected in order to interpret results. This is especially true in considering the necessity for further treatment. An hemolysis test is but one of the links in the chain of evidence. It is therefore believed that better results may be expected if the clinician on whom devolves the responsibility of diagnosis and treatment has, under his supervision, the details and control of such tests and a thorough understanding of the technic.

For example, it has been noted by many workers that tabetics and patients with general paralysis may not give positive hemolysis tests for lues. Such results should not necessarily militate against the tests or, for that matter, against theluetict origin, since these conditions may be only the effects of the earlier, perhaps sufficiently treated, disease. In fact, it is entirely possible, as suggested by Weil, that the luetict toxin makes selective action and that when it attacks the lipid or lecithin constituents of the central nervous system, it spares these constituents of the red cells. This explanation is entirely plausible, for we are not without examples of the selective action of bacterial toxins in other types of infections.

ADVANTAGES OF THE COBRA VENOM HEMOLYSIS TEST

It may seem unnecessary to provide another test for syphilis, but because of certain advantages possessed by the venom test over others in vogue, it may not be out of place to lay stress on its important features. Probably the largest number of tests with this reagent has been made by Corson-White,²³ who has stated that 2,078 cases have been examined. This number included syphilis in all stages (836 cases), controls, cancer, tuberculosis, brain tumors, sarcomata, typhoid, etc. She obtained positive cobra venom tests in 96.2 per cent. of frank visceral and bone syphilis, excluding cerebrospinal lesions. In latent (non-active) cases the results of the test were better than with the Wassermann or the Noguchi modification. She has also found that the test lasts longer in treated patients than other hemolysis tests.

Schwartz²⁴ found, in early cases with little or no treatment, that the complement-fixation test was more sensitive than the cobra-venom test. An average of his figures for the early cases gave 86.9 per cent. positive reactions for the former, and 65.5 per cent. positive reactions for the latter. He found, however, in the later untreated stages of the disease, that the Weil test was more sensitive than the Wassermann.

24. Schwartz: New York Med. Jour., 1912, xcv, 23.

For the late active cases with little treatment, the Wassermann was positive in 77.5 per cent., the Weil in 81.6 per cent. In the late, non-active, untreated cases, the Wassermann was positive in only 34.7 per cent., while the Weil was positive in 76.3 per cent. In nine of the cases reported by Schwartz, there was a definite history of lues and the Wassermann reaction was negative although the Weil test was positive, which shows that the latter test is more sensitive in certain old cases of syphilis.

TABLE 3.—COMPARISON OF WASSERMANN AND WEIL REACTIONS IN ACTIVE AND LATENT SYPHILIS

POSITIVE WASSERMANN REACTIONS		
	Active Syphilis Per cent.	Latent Syphilis Per cent.
Corson-White ²⁵ (836 cases)	88.5	51.7
Schwartz ²⁴ (356 cases)	81.5	42.0
Wassermann ²⁶ (1,982 cases)	90.0	50.0
Fleischmann ²⁶ (192 cases)	93.0	52.0
Swift ²⁷ (344 cases)	87.5	54.1
Cummer and Dexter ²⁸ (490 cases)	90.9	62.8
Average per cent., 4,200 cases	88.5	52.1

POSITIVE WEIL REACTIONS		
	Active Syphilis Per cent.	Latent Syphilis Per cent.
Corson-White ²⁵ (836 cases)	96.2	80.4
Schwartz ²⁴ (356 cases)	69.3	66.1
Stone and Schottstaedt (87 cases)	90.9	87.8
Average per cent., 1,279 cases	85.4	78.1

It has been the experience of those who have worked with the cobra venom hemolysis test in lues, that the test is more sensitive and persists much longer than the Wassermann in treated patients. In fact, it is not at all unusual for a positive Wassermann to become negative after a short course of treatment. We have been convinced personally that many of the patients who a few years ago were pronounced cured, because of the absence of symptoms following faithful mercurial treatment for two or three years, were not cured at all but were merely in the latent tertiary stage of the disease. Many of these would give a positive reaction to either the Wassermann or the Weil test, and a considerable proportion would give a positive Weil reaction and a negative Wassermann.

25. Wassermann: Quoted by Bolduan, "Immune Sera," 1911, p. 198.

26. Fleischmann: Quoted by Bolduan, "Immune Sera," 1911, p. 197.

27. Swift: THE ARCHIVES INT. MED., 1909, iv, 376.

28. Cummer and Dexter: Ohio State Med. Jour., Dec. 15, 1911.

As mentioned by Corson-White and Ludlum,²¹ the number of positive responses to any specific test in tertiary syphilis falls very markedly from the number of responses given during the secondary period, although the results are positive in higher proportion in active tertiary than in latent tertiary syphilis. Such we have found to be the case with the cobra venom test. Figures, however, are apt to be misleading, since it is often exceedingly difficult, if not impossible, to tell whether a patient is afflicted with active tertiary or non-active (latent) syphilis without an hemolysis test. Much depends on the definition existing in the mind of the examiner. We have found the following classification satisfactory, and as such it has been used in the tables.

1. Primary.
2. Secondary.
 - a. active.
 - b. non-active (latent).
3. Tertiary.
 - a. active.
 - b. non-active (latent).
4. Congenital.
 - a. active.
 - b. non-active (latent).
5. Clinically cured.

We have considered all patients with symptoms, such as universal glandular enlargements, mucous patches and roseola as secondary types even though the primary lesion was unhealed. When, after a few weeks or months, such secondary manifestations had disappeared and no symptoms were present, we have classed the type as secondary non-active (latent). If, after a quiescent period varying from a few months to years, symptoms again manifested themselves, we have classed the stage of disease as active tertiary; while if a lapse of a number of years occurred without active symptoms, we have classed the stage of disease as latent tertiary, if the hemolysis tests were positive, or clinically cured if such tests were negative.

The cobra venom test has proved much less laborious and time-consuming in our hands than the complement fixation test of Wassermann, the final readings as clearly cut and the possibility of error less frequent. In a number of instances the test was repeated two or three times on the same patient before beginning treatment, and the final readings were found to be remarkably constant. In fact, on only two or three occasions have the final readings been classed as doubtful, and the tests have not, when full consideration was given to the clinical aspects of the cases, led, to our knowledge, to error in interpretation. On the contrary, a positive Wassermann reaction may lead to confusion in diagnosis. The blood of one patient with erythema multiforme gave positive complement fixation tests made by a colleague, and a negative cobra hemolysis test by ourselves. In this instance the Wassermann test was

positive twice out of three times. The rash disappeared on free purgation and as the patient has subsequently been under observation for seven months, lues can be absolutely excluded.

The cobra test, however, was positive, in our hands, in another patient with morbilliform erythema but did not lead to confusion in diagnosis as other clinical evidences of lues were lacking. Again, in a patient with the clinical history and glandular evidences of pseudoleukemia, the blood gave a positive complement fixation test made by a colleague, while the cobra venom test was negative.

This patient because of the positive complement fixation test was given 0.6 gm. salvarsan intravenously by the attending physician. He developed an edema of the larynx, abundant nucleo- and serum-albumin appeared in the urine, which persisted until death, and the glands rapidly disappeared, as often happens under large doses of any form of arsenic. The glands, however, after a quiescent period of about ten days enlarged again and soon reached their former size. The enlargements persisted until death about ten weeks later, despite vigorous mercurial treatment. It is, of course, possible that this patient had coexistent lues (congenital?) and pseudoleukemia.

CONTROLS

The presence of jaundice has been supposed to interfere with the complement fixation test, but does not, so far as known, interfere with the cobra venom test. Schwartz obtained a positive Wassermann and a negative Weil test in a case of jaundice. Scleroderma, leprosy, polycythemia and scarlet fever have repeatedly given positive complement-fixation tests for lues by competent observers. We have had no opportunity to use the cobra venom test in such cases, but in Weil's reports he mentions negative cobra venom tests in six cases of scarlet fever, two of polycythemia and one of scleroderma. Schwartz, however, obtained positive cobra venom tests in one patient with scleroderma and in another with Raynaud's disease, both of whom gave negative Wassermann tests. He mentions that both these conditions are looked on by many as of luetic origin and that the Wassermann test has frequently been reported as positive in both.

In 129 patients sent to him for diagnosis it was found that the Wassermann and Weil reactions agreed in 124, or 96 per cent. He also found in the examination of seventy-five control patients with various diseases including cancer, tuberculosis, pernicious anemia, pneumonia, erythema multiforme and other skin diseases, chancre, osteomyelitis, periostitis, acute arthritis, hepatic cirrhosis, leukoplakia, scleroderma and sarcoma that all were negative to both tests. In three other patients with advanced carcinoma, in which the Wassermann reaction was negative, Schwartz obtained positive cobra venom tests. Weil has mentioned a positive cobra venom reaction in a patient with gastric carcinoma who subsequently confessed to a syphilitic infection twenty years previously.

Schwartz obtained a negative Wassermann and a positive Weil reaction at the first examination of a patient with Addison's disease. After two weeks of luetic treatment, during which time the patient improved, both tests were positive. The patient probably had a syphilitic affection of the suprarenals.

SUMMARY

In four patients with primary syphilis the cobra reaction was positive in only one, or 25 per cent.

In *twenty-two cases of active* secondary and tertiary syphilis the cobra venom reaction of Weil was positive in twenty, or 90.9 per cent. Of the two which did not give positive reactions, one was negative, while the other gave a "suspicious" reaction. The latter patient had been on mixed treatment for five years with two recent injections of salvarsan. If the test had been made two months, instead of two weeks, subsequent to the last injection of salvarsan the test would, in all probability, have been negative and he would have been classed with the "clinically cured."

In thirty-three cases of *latent* secondary and tertiary syphilis the cobra venom reaction of Weil was positive in twenty-nine, or 87.8 per cent. Of the four which did not give positive reactions, two were negative and two gave "suspicious" reactions. Both of the latter had had mixed treatment for more than one and one-half years with no recent active clinical signs of the disease. They would, under ordinary conditions, have been classed with the "clinically cured."

In twenty clinically cured patients the cobra reaction was negative in all.

At this point we wish to call attention to the figures shown in Table 3. It will be noticed that the average positive Wassermann reactions, as obtained in an analysis of 4,200 cases of active syphilis was 88.5 per cent., while the average positive Weil reactions in 1,279 cases of active syphilis was 85.4 per cent. The two averages are approximately the same. On the other hand, there is a marked difference between the averages, similarly obtained, for latent syphilis. The Wassermann positives in latent syphilis averaged 52.1 per cent., while the Weil positives in latent syphilis averaged 78.1 per cent.

In other words the Weil cobra venom test lasts longer in treated cases than the Wassermann and has given about 26 per cent. more positive responses in latent syphilis than the Wassermann. Such a result is of especial value in the latent stage of the disease when clinically the diagnosis is, for the most part, obscure, and when a laboratory test is most needed to supplement clinical opinion.

In seventeen cases of syphilis, normals, parasyphilis and other diseases (Table 1) the Wassermann and Weil reactions agreed, when blood was used, in fifteen, or 88.2 per cent. One of these was a tertiary active in which the Wassermann reaction was negative while the Weil

test was positive; the other was a case of general paralysis, probably on a luetic basis, with positive Wassermann reaction in blood serum, positive increased globulin test in cerebrospinal fluid and a negative Weil reaction.

In thirteen cases of syphilis, normals, parasyphilis and other diseases, the Weil and Noguchi butyric acid reactions agreed in eleven, or 85.4 per cent.

In our work with forty-three controls a negative Weil reaction was obtained in all but one, a patient with morbilliform erythema.

Fourteen of the controls were patients with tuberculosis in an active stage. In twelve of the fourteen, complete hemolysis took place very rapidly in all tubes in about three hours as contrasted with about twenty-four hours for normal blood. The two bloods which did not hemolyze so rapidly were from patients who confessed to syphilis in earlier years.

In contrast, then, to the hyposusceptible cells of luetic individuals to cobra venom hemolysis, the cells of individuals in an active stage of tuberculosis are apparently hypersusceptible to cobra venom hemolysis. The tubercle toxin appears to so affect the stromata-holding lecithin of the cells as to render it more freely available for the union with cobra venom, the exact opposite of which apparently occurs as a result of the action of the luetic toxin on the lecithin of red cells. This suggestion may be of value in differentiating syphilis and tuberculosis of the lungs in which the clinical diagnosis might not otherwise be clear. Such an instance occurred in Patient 109, who had been under treatment in the dispensary for two years for pulmonary tuberculosis which was supposed to have followed pneumonia eight years before. Tubercle bacilli had never been demonstrated nor had the temperature been above 99 degrees, although signs of pulmonary excavation were present. Lues was denied but the patient improved rapidly under specific treatment.

Addendum: Since this article was completed Kuschakoff,²⁹ working under the direction of Wassermann, has published his comparative results in a series of patients tested with the complement fixation method and the cobra reaction. He concludes that "the phenomenon of retarded hemolysis is present in a considerable portion of cases with syphilis but the cobra reaction is of no practical value unless controlled by the Wassermann reaction." As will be evident from his own figures, such conclusions are not warranted, for in sixty-seven cases of undoubted syphilis only twenty-eight gave a Wassermann positive while thirty-two gave a cobra positive; i. e., 41 per cent. as against 48.5 per cent. In Table 6 of his article he has stated that of fifteen patients infected with syphilis eight to twelve years previously, four were Wassermann positive and eleven were Wassermann negative, while nine were cobra positive and six were cobra negative; i. e., 26.6 per cent. Wassermann positive as against 60 per cent. cobra positive. In eight of his patients who had received intensive treatment the cobra reaction was positive while the Wassermann reaction was negative. In twenty-one controls the cobra reaction was negative in all. It therefore seems far-fetched to describe the Wassermann as a necessary control to the cobra test since his own figures entirely disprove his assertions.

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29. Kuschakoff: *Ztschr. f. Immunitätsf.*, 1912, xii, 532.

THE INFLUENCE OF THEOPHYLLIN ON NITROGENOUS EXCRETION AND PARTITION *

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The general plan of our intended research (which has been interrupted by Dr. Welker's removal from Philadelphia) was to study what changes, if any, could be found in the distribution of the urinary nitrogen after the use of certain typical diuretics, either in healthy persons or in nephritics. As examples of the purin group of diuretics we selected caffein and theophyllin. Our study of the former has been embodied in another article already published;¹ the latter is considered in the present communication. A rather careful survey of the literature of theophyllin has failed to discover any previous study of the nitrogen partition under its influence, though Meinertz² made carefully controlled estimations of the total nitrogen output.

Theophyllin (1,3-dimethyl-xanthin) was discovered in 1888 by Kossel³ in an alcoholic extract of tea leaves from which the greater part of the caffein had been removed. Fischer⁴ synthesized it from uric acid while Traube⁵ made a more complete synthesis (theocin) ten years ago, from which time its general use dates. Administered in therapeutic doses (0.5-1.0 gm. daily) it has been found to produce prompt and profuse diuresis with an increase in the amount of salts excreted. Diuresis may set in within three-quarters of an hour and usually reaches its maximum on the first or second day, occasionally later. Diuresis may be diminished by the second day but usually not until the third or fourth day. It ceases almost immediately on withdrawal but the effect may be renewed by repeating the drug. Caffein and theobromin act more slowly and persistently. It is generally agreed that theophyllin meets its best indication in the passive congestion and edema of heart disease, especially when combined with digitalis. Most clinicians, basing their opinions no doubt on the prevalent theory of its pharmacology, consider it contra-

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1. Farr and Welker: *Amer. Jour. Med. Sc.*, March, 1912.

2. Meinertz: (a) *Therap. Monatsheft*, 1903, xvii, 58; (b) *Ibid.*, 1904, xviii, 275.

3. Kossel: *Ztschr. f. physiol. Chem.*, 1888, xiii.

4. Fischer: *Ber. d. deutsch. Chem. Gesellsch.*, xxx, 549.

5. Traube: Cited by Meinertz (Note 2).

indicated in acute nephritis and of doubtful utility in chronic nephritis. Others take the opposite view. In the ascites of cirrhosis and in inflammatory exudates though not harmful, it is said to be of doubtful efficacy, an opinion consonant with our own experience. The unpleasant or even serious symptoms which occasionally occur have been attributed to disregard of contra-indications, to faulty administration, to too profuse diuresis, to other untoward or excessive physiologic actions, or to accidental or unrelated causes (e. g., epilepsy).

The following are the more common unfavorable or poisonous symptoms that have been described: gastro-intestinal: heaviness in the stomach, nausea, vomiting, slight or severe diarrhea; nervous: excitability, restlessness, headache, insomnia, convulsions, unconsciousness; miscellaneous: faintness, Cheyne-Stokes respiration, uremia, dependent on rapid diuresis. The gastro-intestinal symptoms are evidently due to the irritating local effect of the drug, especially when not properly diluted. One reporter found hemorrhages into the mucous membrane of the stomach at autopsy in one patient and experimentally in the stomachs of animals to which he had administered the drug. This is, however, a solitary observation. The severe purgation described by another author as almost constant has not been observed by us in our cases nor has it been noted in the majority of reports. The more trivial nervous symptoms are evidently due to the physiologic action of the drug, if we may judge by their similarity to those produced by caffeine. Convulsions, which have been reported in fifteen or more cases, are attributed by Schlessinger to the action of the drug itself. He states that if the patient survives the attack and the drug is stopped recovery is the rule. It is likely that in a considerable proportion of these cases the association with convulsions was accidental. Thus, in two of our cases uremic convulsions occurred, but in one case before the drug was administered and in the other long after it had been discontinued. Theophyllin sodio-acetate is said to be more soluble than theophyllin and better tolerated by the stomach.

Theophyllin is not a cardiac stimulant, but its effect on the nervous system is similar to that of caffeine though not so pronounced. Its action on the kidneys though greater is analogous to that of caffeine and theobromin and is shared to a greater or less extent by all the xanthin group, including, in addition, xanthin, paraxanthin, heteroxanthin, methylxanthin, isocaffeine, desoxycaffeine and desoxytheobromin. Theophyllin acts best when the blood-pressure is well sustained, but does not itself seem to have any pressor action. In rabbits there may be a transient rise in the blood-pressure. Its action cannot, therefore, be readily explained by the "mechanical" theory of Ludwig, which attributes diuresis to simple filtration through the capsule of Bowman with subse-

quent concentration by resorption in the convoluted tubes. Most of those who have written on the subject state that it acts by stimulating the specific secretory cells of the capsules and tubules, either because it is an irritant or because it acts as a specific "hormone." Hence they consider it contra-indicated in nephritis. Tigerstedt is credited with the hypothesis that caffein and theophyllin dilate the renal vessels, not through the vasomotors, but by a direct action on the vessel walls. This dilatation increases the flow of blood through the kidney and favors the proper nutrition of the secreting cells and brings the necessary material to them. This hypothesis seems well supported by experiment, whereas there is little evidence to indicate the supposed irritant action of this group of diuretics (occasional transient traces of albumin). Either of the last-mentioned hypothesis harmonizes with the Bowman-Heidenheim theory of secretion which, briefly stated, is that water and salts are excreted through the capsule of Bowman, and urea and other specific materials through the convoluted tubes, etc., but that in both instances there is a specific secretory activity not explainable by simple laws of physics. Theophyllin, according to previous studies, increases the elimination of sodium chlorid and water, but apparently has little or no influence on the excretion of sulphates, phosphates or of the total nitrogen. The tables given by Meinertz² show this admirably. In a normal case with profuse diuresis after the drug a notable increase in the NaCl from 11 to 15 gm. was found with a corresponding retention on the following day. In another case with dropsy there was an even greater elimination of NaCl but no corresponding retention following. It is probable that in the latter case the salt was derived from the dropsical fluid eliminated and did not need to be replaced. In this connection it may be stated that diuresis in normal persons after theophyllin is promptly restricted by the exhaustion of the available supply of fluid, whereas in dropsical cases it may continue for several days. In clinical experiments this error may be obviated by limiting the administration of the drug to one day or by supplying enough water to keep the available supply at a more or less constant level. The latter method does not permit us to exclude the effect of copious water drinking as a cause of the increased flow of urine.⁶

6. Articles consulted in the preparation of the therapeutic and pharmacological summary are as follows:

- Ach: *Arch. f. exper. Path. u. Pharm.*, 1900, xliv, 319.
- Alkan and Arnheim: *Therap. Monatsh.*, January, 1904, xviii, 20.
- Allard: *Deutsch. Arch. f. klin. Med.*, 1904, lxxx, 510.
- Asher: *Therap. Monatsh.*, 1908, xxii, 643.
- Astolfani: *Abstr. Biochem. Centralbl.*, 1905-6, iv, 202.
- Brown: *Northwest Medicine*, January, 1910.
- Chevalier: *Rev. de therap.*, 1903, lxx, 73.
- Cushny: *T. B. of Pharmacology*, Phila., 1906.
- DeMarchis: *Abstr. Biochem. Centralbl.*, 1905, iv.
- Döring: *München. med. Wehnschr.*, 1903, 1, Part I, No. 9.

AUTHORS' EXPERIMENTS

For our cases a uniform diet was employed to secure simplicity and accuracy in administration and at the same time to supply the necessary number of calories and the low proportion of protein desired. Advantage was taken of the uniform size and weight of commercial soda biscuits and sugar lumps to eliminate the tedious daily weighing of the food. The butter was at first cut in blocks of the desired weight and afterward cubes of similar dimensions were used. The orange juice was added at the suggestion of Dr. Riesman to make the diet more palatable. The food was divided into three or four meals to suit the patient's taste.

The "units of 100 calories" referred to in Table 1 were calculated in accordance with the suggestion of Prof. Irving Fisher;⁷ thus, 180 c.c. of orange juice, estimated to contain 24.5 gm. of sugar (carbohydrate), would yield 100 calories (factor for carbohydrate 4.1). Two thousand one hundred and fifty calories were thought sufficient for a man of 70 kilos at rest in bed (30 calories per kilo) or for a man of 50 kilos at light work (40 calories per kilo). The protein was kept at a minimum on account of the character of some of the cases studied.

In each case studied the diet was given for three days before any specimens were collected (period of diet adjustment). Then followed a "normal period" and "experimental period" and, when possible, an "after period" of two or three days each. The urine was collected in bottles sufficiently large to hold the twenty-four hours' secretion to which a suitable quantity of powdered thymol had been added. The volume.

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- Dresser: *Pflüger's Arch. f. d. ges. Physiol.*, 1904, cii, 1.
 Gutman: *Arch. f. Kinderh.*, 1904, xxxiv.
 Hess: *Therap. Monatsh.*, 1903, xvii, 196.
 Hornburger: *Therap. Monatsh.*, 1905, xix, 452.
 Howell: *Text Book of Physiol.*, Phila., 1909, p. 803.
 Hundt: *Therap. Monatsh.*, 1904, xviii.
 Jacobaus: *Therap. Monatsh.*, 1904, xviii, 564.
 Kramer: *München. med. Wehnschr.*, 1903, I, Part I, p. 547.
 Lowenmayer: *Therap. d. Gegenw.*, 1904, iv.
 Loëwi: *Abstr. Biochem. Centralbl.*, 1905-6, iv, 286.
 Meyer: *Therap. Monatsh.*, 1911, xxv, No. 1.
 Minkowski: *Ther. d. Gegenw.*, November, 1902.
 Schlesinger: (a) *München. med. Wehnschr.*, 1905, xxiii, 1095; (b) *Ibid.*,
Therap. d. Gegenw., March, 1903.
 Schmidt: *Cal. State Jour. Med.*, August, 1910, viii, 263.
 Schiemdeberg: *Deutsch. Arch. f. klin. Med.*, 1904-5, lxxxii, 395.
 Schmitt: *Bull. gén. de thérap.*, 1903, cxlvi, 218.
 Siegel: *Berl. klin. Wehnschr.*, 1904, No. 1, 18.
 Sommer: *Therap. Monatsh.*, June, 1905, xix, 285.
 Stein: *Prag. med. Wehnschr.*, 1903, xxviii, No. 16, p. 182.
 Stross: *Wien. klin. Rundsch.*, 1903, xvii, 359.
 Suter: *Korresp.-bl. f. Schweiz. Aerzte*, 1904, vii.
 Theohari and Giurea: *Abstr. Ztschr. f. Biochem.*, 1910, p. 1003.
 Thomas: *Bull. gén. de Thérap.*, 1903, cxlv, 890.
 7. Fischer: *Jour. Am. Med. Assn.*, April 20, 1907.

reaction and specific gravity were taken and the ammonia, nitrogen and creatinin at once determined. At the end of each "period" an "aliquot" portion of each specimen was taken and the other nitrogen estimations made in this mixed sample. The first table in each case showed the daily records; the second the amount of each constituent in terms of nitrogen for each period; the third the calculated average per day for each period, and finally, the percentage of each constituent on the basis of the total nitrogen. In these tables the quantity of ammonia nitrogen and creatinin nitrogen for each period was obtained by getting the average of the daily estimations, whereas the other figures were obtained by one estimation in an aliquot specimen of the whole period. The reason for this difference of method is that the ammonia and creatinin can only be accurately deter-

TABLE 1.—LOW PROTEIN DIET FOR STUDY OF METABOLISM IN NEPHRITIS, ETC.

Amount	Grams of Protein	Units of 100 Calories	Protein Calories	Fat Calories	Carbohydr. Calories
Milk, 1 200 c.c.	40.5	8.5	162	442	246
Butter, 32 gm.5	2.5	2	248	...
Soda biscuits, 260 gm. (32 Unedas) ...	18.0	8.0	72	160	568
Sugar, 48 gm. (6 domino lumps)	2.0	200
Orange juice, 90 c.c.5	50
	59.0	21.5	236	850	1,064
					850
					236
Total calories					2,150

Water 1 liter. Total fluid 2,250 c.c.

mined in the fresh urine, whereas urea, uric acid, etc., remain unaltered in a properly preserved specimen and can be examined as convenience dictates. The methods of analysis used were the same as described by one of us in a previous article.⁸ The recorded figures were in all cases averages of two or more closely agreeing results.

CASE 1.—A normal man, weighing 120 pounds, at light work. On the second day of the experimental period the theophyllin was diminished on account of malaise, dryness of the nose and skin, nervousness, tremor and anorexia.

CASE 2.—A man suffering from neurasthenia but otherwise normal. The same diet was used as in the previous cases but no theophyllin was given. The analyses were made by Dr. G. J. Saxon by whose courtesy I am able to present these results as a control.

8. Ditman and Welker: New York Med. Jour., May 15, 22, 29; June 5, 1909.

CASE 3.—A man, weighing approximately 150 pounds, at rest in bed. The diagnosis was chronic interstitial nephritis complicated by uremic convulsions. Clinically he made a complete recovery.

CASE 4.—A man of average weight at rest in bed. The diagnosis was chronic diffuse nephritis with hypertrophy of the heart, arteriosclerosis, hypertension and generalized eczema. The onset was with severe itching as the dominant if not sole symptom. He died from uremia (convulsions) about a month after the urinary studies were made.

DISCUSSION OF EXPERIMENTS

In the latter two cases the albumin was so small in amount at the time of the examinations that we did not need to take it into account in our estimations, a circumstance that facilitated our estimations very materially.

The detailed histories of these cases as well as the complete analytical tables have been printed in the Philadelphia General Hospital Reports for 1910⁹ and are therefore available for reference. It has seemed best in the present paper for the sake of brevity and clearness to condense these tables into one (Table 2) so as to emphasize the more important points at the expense of somewhat confusing details. The cases and tables have not been numbered to correspond with the hospital record but can be easily identified.

If we compare the average daily quantities as given in Part I of the table a noteworthy diuretic effect is apparent in Cases 1 and 3 and a complete lack of it in Case 4. The unfavorable clinical course of the latter case indicates that this was due to renal insufficiency, possibly aggravated by a stimulus which was as apparently beneficial in Case 3. The diuresis was more prompt and fugacious in Case 1, more slow and persistent in Case 3. If the original tables are consulted it will be found that the patient in Case 1 during the second period excreted 800 c.c. more than would have been the case had the normal average continued, while in the third period there was a corresponding retention, but of less degree. In the third case, if estimated in the same way, 500 c.c. more were excreted in the three experimental days than would otherwise have been the case. In the fourth patient there was an even more striking effect in the opposite sense. It will be recollected that this patient did not improve on this or any other treatment and eventually died of uremia.

The average daily *total nitrogen* is shown in the column marked Part II, Cases 1 to 3, ranging from a minimum of 8.0 to 8.7 gm., probably represent normal variations on the diet given. In Cases 1 and 3 there was a slight diminution after theophyllin, whereas Meinertz² found a similar slight variation in the opposite direction. This would seem to verify his conclusion that the alteration was too slight to merit attention. In Case 4 the total nitrogen during the "normal period" was less, while

9. Riesman, Welker and Farr: Philadelphia General Hospital Reports, 1910.

TABLE 2.—COMBINED TABLE, SHOWING RESULTS OF AUTHORS' EXPERIMENTS

Cases	Periods	Part I		Part II		Part III. Average Percentage Findings on Basis of the Total Nitrogen					
		Average Daily Quantity c.c.		Average Daily Total Nitrogen gm.		Ammonia Nitrogen	Urea Nitrogen	Uric Acid Nitrogen	Purin Base Nitrogen	Creatinin Nitrogen	Nitrogen Undeterm'd
1. Normal	Normal Theophyllin, 1.0 gm. daily	1525		8.69		2.50	86.92	0.70	0.00	4.56	5.31
1. Normal		1924*		8.13		2.37	87.03	0.47	0.34	4.85	5.00
1. Normal	After Period	1236		8.17		3.53	81.00	0.89	0.12	5.02	9.44
2. Normal			8.46		3.28	84.79	0.25	0.92	3.99	6.75
3. Nephritis	Normal or Control	2143		8.61		5.18	76.76	1.29	0.17	5.46	11.12
3. Nephritis	*
3. Nephritis	Subperiod, specimens discarded	2610		7.96		4.84	84.96	1.04	0.55	5.68	2.79
4. Nephritis	Theophyllin, 1.0 gm. daily	1452		7.01		2.73	82.98	0.23	0.40	4.07	9.61
4. Nephritis	Normal	1200		5.37		2.60	84.91	0.28	0.43	4.23	7.56

*First day, 2,228 c.c.; second day, 1,621 c.c.

after theophyllin it was very much reduced. This was probably an expression of renal insufficiency, possibly aggravated by the drug.

Part III of the table shows the percentage findings of the various constituents on the basis of the total nitrogen. The ammonia nitrogen was fairly constant for each case though absolutely high in Case 3. The urea in the third period of Case 1 was moderately diminished relatively, and the undetermined bodies (and to a less extent the ammonia) increased. This was parallel with, and possibly dependent on, unpleasant symptoms produced by the drug. In Case 3, on the other hand, the urea nitrogen was low in the preliminary period and the ammonia and undetermined nitrogen percentages high. In this case the metabolism apparently became normal under theophyllin, though not necessarily because of it.

The uric acid and purin body nitrogen was low in all the examinations on account of the character of the diet. In Cases 2 and 4 the uric acid was very small in amount, but there was a corresponding increase in the purin bodies. The creatinin was practically uniform for each patient in accordance with the usual experience.

CONCLUSIONS

In conclusion it may be stated that theophyllin promoted the excretion of fluid in two of our cases but apparently did not affect, or even slightly diminished, the excretion of nitrogen. In a case of diffuse nephritis (Case 4) diuresis failed to develop and the nitrogen elimination was sharply reduced.

In a case of chronic interstitial nephritis (Case 3) the urinary partition was apparently changed by the drug so that it approached more nearly the normal. This may have been due to natural causes incident to convalescence.

The slight or doubtful influence of theophyllin on nitrogen excretion and its pronounced influence on the excretion of water and sodium chlorid² suggest that this substance may act principally on the capsule of Bowman and little if at all on the tubules (Bowman-Heidenhein theory). Its failure to act in Case 4 might then be attributed to extensive involvement of the glomeruli¹⁰

The work described in this paper was suggested by Dr. David Riesman, who also permitted us to use his wards at the Philadelphia General Hospital. We desire to express here our appreciation of his kindly interest.

10. Suggestion of Dr. H. C. Wood, Jr., in the discussion.

PRELIMINARY PAPER ON SOME UNFAMILIAR AND SOME NEW PERIOSTEAL REFLEXES *

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The reflex activity of the nervous system is one of its most remarkable properties, and as such has engaged the earnest attention of scientists. On the clinical side the discovery of reflex pupillary changes in disease, particularly the phenomenon of Argyll-Robertson and the elicitation of the knee-jerk by Erb and Westphal, opened up a field of research work the results of which make up a large part of our present day neurological diagnostic means. The discovery of the ankle-jerk by Gowers and the establishment of its great clinical value by Sarbo, Ziehen and others; the remarkable great-toe phenomenon of Babinski and its modified forms as elicited by the technic of Oppenheim and Gordon, stimulated a great many workers and at the present time almost all the cutaneous surfaces and tendons have been searched for characteristic reflex phenomena.

A group of reflexes which has with all this research activity received only scattered and isolated attention and has not as yet been incorporated into routine neurological investigation is the so-called periosteal group. Without here going into the complete history of the work done in this field, it is interesting to note that Erb recorded a few of these reflexes as did Strumpell, Sternberg and others of the pioneers in reflex researches. In later years a few workers have systematically investigated this or that group of periosteal reflexes — notably Valobra and Bertolotte, Noica and Strominger in France, Hirschberg, Keller, Huisman, Forster and others in Austria and Germany as well as Bechterew in Russia.

Since the reflex function of the body may fail at one place and yet be well preserved and even exaggerated in another, for example, as the ankle-jerk often fails before the knee-jerk in tabes, or as the Argyll-Robertson pupil may be associated with lively arm reflexes and absent knee-jerks, or in the often noted dissociation of tendon and skin reflexes, so, *a priori*, the periosteal reflexes stand out as at least a fitting subject for research. It was this consideration that led me over a year ago to include in my routine neurological work the study of the reflexes obtained from certain bony areas and this paper is a preliminary report of some of the results.

*Manuscript submitted for publication, April 19, 1912.

*Read before Medical Sciences Club, St. Louis, March 12, 1912.

The reflexes to be considered are as follows:

1. One, or rather a series, obtained by tapping with the ordinary reflex hammer and with moderate force the ulnar styloid process. This is best obtained with the patient lying on his back, his elbow flexed at an obtuse angle and resting on his body. It goes without saying that in all reflex examinations the patient must be as nearly relaxed as possible, and the parts stimulated and those reacting must be bare. Without stripping the parts examined no scientific accuracy can be claimed for any examination.

Following this stimulation there results: (*a*) a contraction of the triceps described by Bechterew, a quick sharp contraction often untended by movement of the arm; (*b*) a contraction of the posterior fibers of the deltoid, which occurs about as often as Type A; (*c*) a combination of both these; (*d*) when the response is very active, the reflex spreads to the supraspinati and infraspinati, the rhomboids, the trapezius and the biceps. In general this reflex is an extensor response and may well be contrasted with that obtained from stimulation of the radial styloid which is a flexor response with contraction either of the supinator or biceps, or both, and in some cases spreading to pectoralis, anterior fibers of the deltoid — the well known and routine radial reflex.

I have described the ulnar styloid reflex as if its reflexogenous zone were limited to the bony process named, but as a matter of fact the reflex may be elicited from any part of the ulna and even from the carpus and metacarpus. However, it is best elicited from the styloid, and as one goes up the forearm the type of reflex changes somewhat.

2. A series of homolateral and contralateral adductions or responses obtained from different bony points of the lower limb. Most of these have been sporadically described; some have been systematically studied, but no one, so far as I know, has noted the relationship existing between the force and frequency of homolateral and contralateral reflexes as obtained from each bony point. In addition, one at least of the sites of stimulation is here described and one or two others here receive their first systematic treatment.

The technic is simple. The patient or subject lies on a table, his bare limbs symmetrically disposed, moderately abducted at the hip and in general in an easy, natural, relaxed attitude. In some cases it is necessary to rotate the leg slightly outward. Percussion of certain areas gives the following responses:

A. A homolateral adductor obtained from the internal condyle, the most common response.

B. A contralateral adductor, obtained from the same spot, always accompanied by the homolateral, much less common and generally less lively.

C. A homolateral obtained from the anterior surface of the tibia, best elicited from the middle of the shaft, somewhat sharper than the internal condylar response and nearly as frequent.

D. A contralateral from this area generally accompanied by the homolateral and less active than it.

Therefore the contralaterals from these two points are constantly accompanied by a homolateral of somewhat greater force and of much greater frequency. I have not been able to determine whether there was any difference in the time of inception. The homolateral and contralateral responses have been described, but their relationship does not seem to have been observed and seems to me to be interesting, to say the very least. It will be noted that their relationship is in accord with Pflüger's laws regarding the spread of reflexes.

E. A homolateral obtained from the external condyle.

F. A contralateral from the same area, more common and generally more lively than the homolateral, thus reversing the rule of the previous reflexes. These external condyle reflexes, if described, have not been systematically studied.

G. A homolateral from the sole of the foot, always accompanied by

H. A contralateral from the sole much livelier and of more frequent occurrence than the homolateral. That is, in my observation the contralateral often exists alone but never the homolateral. This reflex was described by Hirschberg and extensively studied by Valobra and Bertolotte as well as by Keller. It is more common than the external condyle response but less common than the first two groups described.

I. The anterior superior spine gives a contralateral adductor response as well as a homolateral, the first being generally livelier. This reflex was pointed out to me by Dr. W. W. Graves. The crest of the ilium near it gives a homolateral response which is livelier than the contralateral less frequently elicited. These reflexes I have not studied extensively and they are possibly rarer than the rest.

These periosteal reflexes are best elicited from the areas mentioned but where they are at all lively the reflexogenous zone is much broadened. For example, the tibial site often spreads until it includes the internal condyle and the dorsum of the foot. It is curious to note that down to the very sole of the foot the homolaterals will be livelier than the contralateral, but as soon as the sole is percussed the relationship is reversed. The change of type is marked as one passes from the internal to the external condyle and the same is true of the spine of the ilium as compared with the crest. Indeed, while as previously mentioned the internal condyle and tibial response seem to prove Pflüger's law that where homolateral and contralateral responses are elicited from any site the former is more lively than the latter, the external condylar, the sole and the

iliac spinal responses show that it is by no means the universal rule. This discrepancy between so-called laws and facts was pointed out by Sherrington and by Lewandowsky as a result of their animal experiments.

It is necessary at this juncture to point out a factor which often changes the above-described relationship of the contralateral and homolateral responses. It has been assumed in this description that the reflexes are equal on both sides. If, however, the reflexes on the one side are livelier than on the other, then it sometimes occurs that all the adductor responses of that side, whether elicited from bony points on that or the opposite side, will be the livelier.

I have studied these reflexes in correlation with all the routine reflexes of arms, lower extremities, pupils, with Babinski, Gordon, Oppenheim, with the skin reflexes and sensation, with the conditions of the thyroid gland, the cardiovascular system and the bony framework, particularly the shape of the scapula (scaphoid scapula of Graves) as well as in about 100 cases in which spinal puncture and Wassermann reactions were done—in other words, with the whole individual, as emphasized by Graves. In a later paper I shall analyze my results and discuss the physiology of these reflexes, but at present I shall content myself with a few general correlations.

INCIDENCE IN HEALTH

To this end I examined sixty-two medical students of St. Louis University. Briefly summarized the results were as follows:

A. About 25 per cent. showed none of these reflexes. The tendon reflexes were generally moderate; in some cases there was absence of the radial response; in others the knee-jerk was elicitable by reinforcement. Others represented the finest physical types examined.

B. About 60 per cent. gave either a homolateral, or tibial and internal condyle adductor, generally both, and most of these individuals also gave an ulnar styloid. In none of these cases were the reflexes more than moderately lively and the zones of elicitation were rather limited. The reflexes were generally lively.

C. About 10 per cent. gave weak or an occasional contralateral sole response. The tendon reflexes were generally livelier than the group just described.

D. Of the sixty-two men, four gave marked contralateral external condylar, sole, etc., responses. One of these had by his history a typhoid myelitis three years before; two had very large and pulsating thyroids and showed signs of "hyperthyroidism," and one had signs of nervous disease, pupillary anomalies, etc. In other words, these four cannot be called normal, healthy men.

GENERAL CORRELATION WITH THE TENDON REFLEXES

1. All observers agree that the activity of these reflexes is in direct relationship with that of the tendon reflexes; i. e., they are active when the latter are active, diminished or absent when the tendon reflexes diminish or disappear.

2. If the tendon reflexes are equal, then the periosteal reflexes are generally equal, although occasionally there is a discrepancy.

3. If the tendon reflexes are unequal then the periosteal reflexes are unequal. This needs, in the case of the adductors, an illustration. If, for example, the right knee-jerk is livelier than the left, then the right homolateral adductor responses will be greater than the left and, moreover, the contralaterals elicited from the left side will be livelier than the left contralaterals elicited from the right side.

4. In regard to the adductor responses, it may be stated that they have no relationship to the ankle-jerk, since they may exist when these are absent, provided the knee-jerks are lively, as happens in incipient tabes. On two occasions I have seen this remarkable phenomenon — ankle-jerks absent, tapping the Achilles tendon gave very lively adductors. Now while homolaterals and contralaterals are often elicited with the ankle-jerk from the tendon, their occurrence without the tendon reflex is certainly a significant phenomenon.

5. These reflexes have no relation to Babinski, except as lively tendon reflexes have.

GENERAL CORRELATIONS WITH DISEASE

1. These reflexes are very prominent in diseases of the cortex, particularly in uncomplicated general paresis. They are often exquisite in cerebral arteriosclerosis and in both these disease types the zones of elicitation are very extensive.

2. In diseases of the pyramidal tract they are marked. In uncomplicated hemiplegia they are present on both sides but greater on the affected side, provided no great degree of contraction of the adductors interferes.

3. In full-fledged tabes they are absent. In pre-ataxic tabes, with retention of the knee-jerks, they are often very lively, particularly the homolaterals and the contralateral sole. This is in line with the view that there is a stage of increased reflexes in tabes.

4. In exophthalmic goiter they are often very much in evidence, which is in line with the other apparently irritative phenomena. In people with large goiters without definite symptoms they are less frequent.

5. In neurasthenia the homolaterals may be prominent but where the contralaterals, particularly of the external condylar and the iliac spinous are present, and where the reflexogenous are broadened, a close, searching physical examination will generally show the neurasthenic state to be merely a symptom of graver nervous disease.

In conclusion it may be said that these periosteal reflexes are interesting and therefore merit investigation. Moreover, in the case of those described they are elicited from easily accessible surfaces and should be incorporated into routine examinations because in every case they offer just so much additional information regarding the reflex irritability of the patient.

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A CONSIDERATION OF THE PANCREAS AND ITS DUCTS IN CONGENITAL OBLITERATION OF THE BILE-DUCTS *

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Congenital obliteration of the bile ducts is a rare disease, but hardly sufficiently uncommon to warrant the report of a single case, unless it presented unusual symptoms, or served as the ground-work for some new conception of the symptomatology, pathogenesis, or pathology of this obscure condition. The excuse offered for this presentation of a case is that the application of a new method of study during life led to a somewhat broader point of view of this pathological condition. In the course of a clinical study, carried on at intervals for about six weeks on an infant afflicted with this condition, the duodenal catheter was frequently employed, in order to obtain information as to the excretion into the intestine of bile as well as of the pancreatic ferments. This catheter has been described in connection with a study of spasm and stenosis of the pylorus,¹ of icterus neonatorum,² and of the flora of the duodenum in infants,³ so that it is not necessary for the technic to be again reviewed in detail. The accompanying cut (Fig. 1) shows the simple apparatus, which consists of an ordinary Nélaton No. 15 (F.) catheter, marked in an appropriate manner, and of a glass aspirating bulb. As has been stated in previous articles, this catheter can be readily and rapidly passed into the stomach, and through the pyloric sphincter into the duodenum, in infants, from the day of birth to the age of about 2 years. By this means bile and the ferments of the duodenum and pancreas may be obtained for examination.

REPORT OF CASE

M. E. was admitted to the hospital Dec. 19, 1911, when 7 weeks old.

Family History.—First child, pregnancy and delivery normal; no history of miscarriages.

Present History.—History of early and increasing jaundice; exact date of onset uncertain; nursed by mother irregularly.

Examination.—At date of admission the infant was markedly yellow, fairly well nourished, weight 9 pounds 4 ounces. Liver at level of umbilicus. Spleen one finger above crest of ilium, edge sharp and soft. Lungs, heart, and general abdominal examination negative. Urine negative, except for large amount of

*From the Research Laboratory, Department of Health, New York City.

*Manuscript submitted for publication May 21, 1912.

1. Hess, A. F.: Am. Jour. Dis. Child., 1912, iii, 133.

2. Hess, A. F.: Am. Jour. Dis. Child., 1912, iii, 304.

3. Hess, A. F.: Jour. Infect. Dis., 1912, x, No. 5.

bile pigment. Stools clay colored. Blood examination showed 6,000 leucocytes, 65 per cent. mononuclear cells, 35 per cent. polynuclears.

December 20. Child being nursed every four hours. To-day traces of blood following rectal irrigation.

Duodenal catheter passed 1½ hours after nursing, and 2 ounces of uncoagulated milk evacuated. Duodenum easily entered, and 3 c.c. of fluid obtained in the course of one hour, slightly acid, and faintly bile-tinged. Stool clay colored with traces of bile.

December 21. Catheter passed a few minutes after nursing. Stomach contents acid, Congo ++. Duodenal contents contain slight amount of bile and food strings (Cannon).

December 22. Jaundice more intense. Catheter passed five hours after nursing. Stomach empty. Duodenum empty after twenty-five minute test.

December 23. Catheter passed three and one-half hours after nursing. Stomach empty. Duodenum empty after a one-half hour test.

December 24. Condition the same. Catheter passed an hour after nursing. Acid, Congo + milk evacuated. Mucoid fluid containing some bile found in duodenum.

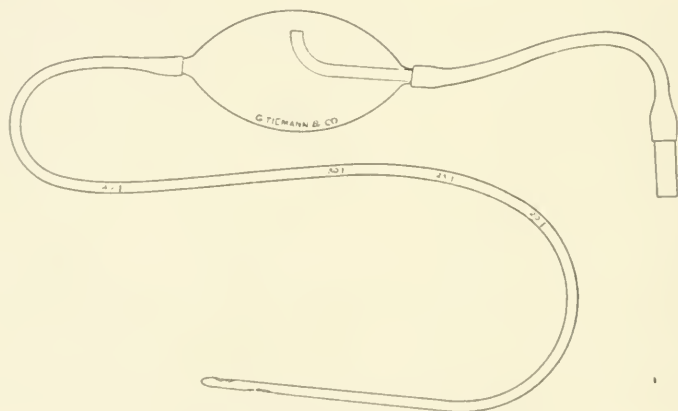


Fig. 1.—Infant duodenal catheter.

December 25. Jaundice increased. Infant sleepy. Catheter passed an hour after nursing. About 1 ounce of very acid, Congo + fluid removed from stomach. Small amount of acid mucus obtained from duodenum.

December 26. Condition the same. Some bile tinged mucus aspirated from duodenum.

December 27. Condition worse. Increased jaundice. Some blood in stool, also subcutaneous hemorrhages. Rectal examination showed a considerable amount of dark fluid blood.

Catheter passed three fourths of an hour after nursing. Congo +++ fluid obtained. About 0.3 c.c. of slightly bile-tinged fluid obtained.

December 28. Coagulation time of blood diminished (15 minutes). Temperature has ranged between 98 and 100 degrees. Weight 9 pounds 2 ounces; that is, only slight loss. Hemorrhages from bowel persist. An operation considered, but thought not advisable.

December 31. Subcutaneous injection of horse serum.

Duodenal catheter passed two hours after nursing. Congo ++ fluid aspirated from stomach, and in ten minutes about 1 c.c. of neutral fluid containing traces of bile obtained from duodenum.

January 2. Child drowsy. Hemorrhages the same. Taken away from hospital against advice.

The child was not seen again for about one month. On February 5 I was sent for and saw it at its home. Although it had lost weight it looked comparatively well and the hemorrhages had ceased. The child was being fed on condensed milk every three hours.

February 7. Doing poorly; has been vomiting; vomiting expulsive in nature. Stool still clay colored. Catheter passed; Congo +++ fluid evacuated from stomach. Marked cardiospasm, and great difficulty in entering stomach. (Probably food has not entered stomach.) Also difficulty in entering duodenum; "accessory method" has to be resorted to. Duodenal feeding with whey.

February 8. Still vomiting, as yesterday. Stool brown (starvation). Catheter passed. Cardiospasm the same, pylorospasm less. Duodenal feeding. Patient readmitted to hospital.

February 9. Doing poorly. Vomiting continuous. Cardia and pylorus less spastic. Duodenal feeding.

February 10. Exitus.

Clinically, the case was clearly one of congenital obliteration of the bile-ducts, showing intense jaundice, marked enlargement of the liver and spleen, and subcutaneous and intestinal hemorrhages. The urine contained a large amount of bile; the stools, although clay colored, also showed traces of bile. The duodenal catheter was frequently passed and determined the presence of bile in the duodenum, and also of the pancreatic ferments in the fluid which was aspirated. The infant did fairly well for three months and then suddenly developed vomiting which was followed by inanition and death. The cause of this vomiting could not be definitely ascertained. Possibly it was due to some error in feeding. It was markedly expulsive in nature, and characterized by cardiospasm, pylorospasm, and a hypersecretion and hyperacidity of the gastric juice.

An autopsy was performed by Dr. Eli Moschcowitz, whom I wish to thank for the following report:

AUTOPSY PROTOCOL

MACROSCOPIC

No. 2764. Heart and lungs not removed.

The liver weighs 170 gm. (formalin). Contour normal; consistency firm. Stained deeply bile-green. Surface roughened. On section the liver is deeply bile-stained; the cut surface shows green lobules with narrow, white spaces intervening. The lobules are slightly elevated; the white portions appear fibrous, and are situated at the periphery of the lobules in the portal spaces. The gross picture corresponds to that of a typical periportal cirrhosis. The remains of the ductus venosus enters the liver through a deep fossa hollowed out of the anterior border. There is a corresponding fissure on the under surface.

The fissure for the gall-bladder is at its normal site, and is occupied by a rather thick mass of fibrous tissue. In this mass there is a small cavity (the gall bladder) running longitudinally for a distance of about 2 cm. The lumen admits a narrow probe, and contains a few drops of clear watery fluid. The finest bristle passed from the gall-bladder in the direction of the cystic duct fails to find an exit.

The ducts of the liver are completely obliterated, and are represented by dense strands of fibrous tissue. The right and left hepatic ducts are impervious

up to the point where they emerge from the liver, as well as the common hepatic duct.

The strand representing the common bile duct is somewhat thicker than the others, and passes to the posterior surface of the duodenum.

On the intestinal wall corresponding to the attachment of this strand, is a small papilla within the lumen (to be described below).

The portal vein and the hepatic artery occupy their normal situations, and show no abnormality in size. There are a number of small lymph-nodes at the base of the fissure for the gall-bladder.

The duodenum is normally situated. Within the lumen and on the posterior aspect are two papillae. The lower one, wider and deeper, is found to be the opening of a pancreatic duct, and into this a fine bristle can be passed. The upper papilla is situated about 2 cm. distant and corresponds to the attachment of the fibrous remnant of the common duct, above described. This papilla is impermeable to the finest bristle.

The stomach, intestines, spleen, mesentery, kidneys, genito-urinary tract and the adrenals are normal; except for rather intense bile staining.

Anatomical Diagnosis: Complete obliteration of all the extra hepatic bile ducts and the papilla of Vater. Hypoplasia of the gall-bladder. Bile pigmentation of the liver, with periportal cirrhosis. Anomalous insertion of the ductus venosus. Anomalous position of accessory pancreatic duct (Santorini) below papilla of Vater.

MICROSCOPIC EXAMINATION

Liver: Under the low power the liver presents the typical appearance of rather advanced periportal cirrhosis. The connective tissue is abundant, loose, moderately infiltrated with round cells, and surrounds many of the lobules completely.

Interspersed in this connective tissue are abundant newly formed bile ducts, similar to those found in the cirrhosis of Laennec.

These ducts are very narrow, anastomose, and in only a few instances can a lumen be demonstrated: the lumen is empty.

Distinct transitions between the liver trabeculae and the newly-formed bile ducts can be demonstrated in many instances.

The hepatic artery and the portal vein in the capsule of Glisson are normal, but no well formed bile-duct is present. There are nowhere evidences of cystic dilations of the bile-ducts. The cells of the liver trabeculae stain well; the nuclei are distinct and reticular. The intra- and intercellular bile capillaries are everywhere dilated and filled with green bile. These dilations are especially prominent in the central portions of the lobule. A noteworthy picture is the occasional appearance of a trabecula of the acinus gland type: the cells are arranged concentrically in a single row around a blood capillary. Such formations are few in number.

Section of the hypoplastic remnant of the gall bladder reveals merely a dense fibrous structure, lined by a single layer of low cuboidal epithelium which is thrown up in low folds.

There is no structure corresponding to the submucosa or muscle fibers of the wall.

Section of the fibrous strands of the obliterated ducts shows nothing in any way suggestive of epithelium or lumen. These strands consist merely of dense fibrous tissue, with a few nerves and small blood-vessels.

Section of the upper papilla reveals this to be a small accessory pancreas in the wall of the duodenum. Serial sections reveal no evidence of a lumen, or of inflammatory tissue.

Sections of the other organs reveal nothing noteworthy. Pancreas normal; no cirrhosis.

DISCUSSION OF AUTOPSY REPORT

The autopsy therefore confirmed the clinical diagnosis of congenital obliteration of the bile ducts. All the extra hepatic ducts were found obliterated. The usual changes in the liver following marked stasis were present. The only notable features were the very exceptional site of entrance of the accessory pancreatic duct (Santorini) in the duodenum, which was below instead of above the papilla of Vater, and the accessory pancreas found in the wall of the duodenum at the site of the papilla of Vater (Fig. 2, a). On opening the duodenum this was seen as a small nodule, resembling one of the solitary lymph-nodes commonly found in the lower intestine. Its true nature was not suspected. It was submitted to serial section with the purpose of ascertaining whether inflam-



Fig. 2.—Obstruction of common bile-duct and pancreatic duct. a, accessory pancreas at site of papilla of Vater; b, opening of accessory pancreatic-duct (Santorini) below papilla of Vater; c, connective tissue representing common bile-duct; G. B., rudimentary gall-bladder; L, liver; St., Stomach; Sp., spleen; D, duodenum.

matory tissue could be found at this point, as it is still an undecided question in the pathogenesis of this disease, whether the obliteration of the bile-ducts is due to a fetal inflammatory process, or to a developmental anomaly. No sign of inflammatory tissue was found on microscopic examination. The glandular arrangement of some of the liver strands, called attention to by Finkelstein,⁴ is also worthy of mention.

4. Finkelstein, H.: *Lehrbuch d. Säuglingskrankh.*, 1912, Part II, p. 438.

EXAMINATION OF DUODENAL FLUID

In the clinical report mention has been made of examinations for pancreatic ferments carried out on the fluid aspirated from the duodenum. Quantitative and qualitative tests were made for the presence of trypsin, 5 per cent. gelatin being used for this purpose; for the tests for amylase a 1 per cent. starch solution was used, and after forty-eight hours the mixture was titrated for sugar by means of Fehling's solution; neutral ethyl butyrate was used to test for lipase, and after twenty-four hours the acidity was determined by means of titrating with twentieth-normal sodium hydroxid. All solutions were rendered alkaline by means of sodium hydroxid, and sterile by the addition of toluol. It does not seem necessary to describe these methods in detail, as an article soon to be published treats of a large series of tests made on infants by this means. It was found in this case that all three pancreatic ferments were being excreted into the duodenum. The trypsin was in considerable quantity as it digested gelatin within twenty-four hours. The amylase was likewise found not insufficient compared with the results obtained on normal infants. The lipase was, however, found to be diminished. Whether this was due to the lack of bile in the duodenum, which, as is well known, intensifies the action of the pancreatic fat-splitting ferment, or whether there was, in fact, a deficiency of lipase, it is difficult to say without further study. The stool contained a large amount of fat, as is the case in all instances of obstructive jaundice.

Cases with obliteration of the common bile-duct usually have been classified according to the obstruction of the hepatic ducts, the cystic duct, or the presence or absence of the gall-bladder. It would seem that this classification can possess no clinical or pathological significance where the common bile-duct is absolutely impervious. It would appear, however, by no means of purely academic interest to ascertain whether the pancreatic ducts are patent or likewise obstructed. In view of the fact that when the common duct is obstructed by a biliary calculus situated at the papilla of Vater, the pancreatic duct frequently is also obstructed, resulting in acute or chronic pancreatitis, it is remarkable that in the pathological condition which we are considering no attention whatsoever has been paid to the pancreas. In a rather extensive review of the literature I have not met with an instance in which the pancreas has been described at autopsy or later examined microscopically. For example, in Thomson's⁵ excellent monograph, published in 1892, which carefully reviewed forty-nine cases, in Beneke's⁶ report of 1907, which considered seventy-four cases, in reports of cases by Murchison,⁷

5. Thomson, J.: Congenital Obliteration of the Bile Ducts, 1892.

6. Beneke, R.: *Kongenitale Atresia d. grossen Gallengänge*, Marburg, 1907.

7. Murchison: *Diseases of the Liver*, 1885, p. 422.

Schueppel,⁸ Henoch,⁹ Rolleston,¹⁰ and many others, no attention has been paid to the pancreas or its ducts. Indeed, the only mention which I have found on this subject was one by Wilks¹¹ in a report published in 1862, which states that "in the duodenum the opening of the bile-duct was found as usual and a probe passed freely into the pancreas." In almost all of these cases the obliteration of the common bile-duct included the papilla of Vater, which is known generally to harbor the outlet of the pancreatic duct as well as of the bile-duct. In these cases, unless there existed another duct from the pancreas to enable it to pour its ferments into the intestine, there must therefore have been in addition to an obstruction of the bile an obstruction of the external secretion of the pancreas. It is difficult to state in just what percentage of cases an accessory pancreatic duct, the duct of Santorini, enters the intestine separately. Opie¹² dissected 100 cases in order to investigate this subject and came to the practical conclusion that "in at least a third of all individuals the duct of Santorini cannot act as an accessory outlet when the duct of Wirsung is occluded."

CONCLUSIONS

In the pathologic condition termed congenital obliteration of the bile-ducts, the common bile-duct has been found almost invariably obliterated in the greater part of its course, including in almost every instance the duodenal end and the papilla of Vater. Into this papilla the main pancreatic duct almost always enters, and accordingly is subjected at the same time to absolute obstruction, so that it would seem preferable to term this disease congenital obliteration of the common bile-duct and pancreatic duct. A classification from a clinical point of view better than the purely anatomical one generally made use of would seem to be to divide this pathologic condition into two main groups of cases: (1) where associated with the obliteration of the common bile-duct there is an obliteration of pancreatic duct, which, however, is compensated for by the fact that the accessory duct, the duct of Santorini, is present and able to excrete the pancreatic ferments into the duodenum;¹³ another group (2) where the obliteration of the excretory apparatus of the pancreas is total and complete, as not only is the duct of Wirsung absolutely obstructed, but no accessory pancreatic duct exists. Cases of congenital obliteration of the common bile-duct and pancreatic duct can, therefore,

8. Schueppel: *Arch. f. Heilk.*, 1870, p. 78.

9. Henoch, E.: *New Syd. Soc. Tr.*, i. 28.

10. Rolleston, H.: *Diseases of the Liver*, 1905.

11. Wilks: *Tr. Path. Soc. London*, 1862, p. 119.

12. Opie, E.: *Am. Med.*, 1903, p. 996.

13. Under this group would come those exceptional cases in which the common bile-duct and the duct of Wirsung enter the duodenum separately and at different levels.

be divided into those with compensated or with uncompensated pancreatic obstruction. The case described in the foregoing pages was of the compensated variety, which comprises the larger group. During life the three pancreatic ferments, trypsin, amylase, and lipase, were repeatedly found in the duodenal fluid obtained by means of aspiration with the duodenal catheter, and the diagnosis of compensated pancreatic obstruction was substantiated after death by finding the main pancreatic duct obliterated and the accessory duct patent.

It is of interest to note that notwithstanding the absolute closure of the common bile-duct, bile was demonstrated in the duodenal fluid and in the stool, proving the probable excretion of bile from the circulation through the intestinal wall. The infant lived for three months, and died as the result of inanition brought on by an acute attack of vomiting accompanied, as tests by means of the catheter showed, by cardiospasm, pylorospasm, and hyperacidity and hypersecretion of the gastric juice. This complication may bear no relation to the underlying pathologic disturbance; reference to the literature in regard to this point, however, shows that marked vomiting has been an important intercurrent symptom in many cases, so that attention should be directed to this complication in the future.

It is probable that it will be found that the cases of congenital obliteration of the bile-ducts associated with uncompensated obstruction of the pancreatic ducts are the more serious, and that infants in this group survive for a shorter period than those in whom the ferments gain entrance to the duodenum by an accessory duct. A test of all cases by means of the duodenal catheter will permit of a clinical classification during life of the compensated and the uncompensated cases; and the data obtained by this means should be carefully correlated with the results of post-mortem examination, especially with the pathological condition of the ducts and parenchyma of the pancreas, an organ which has been absolutely disregarded in the consideration of this disease.

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A COMPARISON OF PHYSICAL SIGNS AND X-RAY PICTURES OF THE CHEST IN EARLY STAGES OF TUBERCULOSIS *

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GENERAL CONSIDERATION OF THORACIC ACOUSTICS

Within the past year it has occurred to one of us to become acutely impressed with the necessity of making an absolute diagnosis in a series of cases presenting rational evidences of pulmonary tuberculosis. Physical examination of these persons disclosed none of the signs usually depended on for the apprehension of incipient lung disease, but the clinical history of lessened energy, susceptibility to fatigue, digestive disturbance, occasional afternoon temperatures and various other accompaniments of failing health plainly indicated a serious constitutional disturbance which, if tuberculous, implied an active undermining of powers which it was of vital importance to check at once. Fortunately, at this time there was under observation a patient whose chest was negative to even expert examination — pursued along catholic lines — although tubercle bacilli had for a while appeared in his sputum a few months previously and his clinical condition remained very unstable.

A careful study was made of this patient to determine whether any definite physical signs were associated with the advent of tuberculous infiltrations. The results were positive to a gratifying degree. It was found that changes in the resonance of voice or whisper could be detected by stethoscopic auscultation when the alterations of physical structure within the chest eluded other means of examination. The auscultatory changes referred to included an estimation of the quality, the intensity, the pitch and especially the duration of the audible vibrations, as well as their distribution over the chest. Obviously, nothing new is contained in these mere statements; nevertheless, one of us (H. S.) can certify that in his own experience a special study of physical diagnosis through many years has failed to achieve a tithe of the certainty in the detection of minute changes in the lungs which the proper application of this method confers. From the theoretical point of view it is obvious that the acoustic phenomena of the chest must respond to every alteration in the thoracic contents. It only remains for practical purposes to discriminate the vocal attributes of definite organic changes.

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The vibrations of the vocal cords which produce voice are transmitted in all directions with an intensity dependent on the continuity and elastic properties of the conducting tissue. The air stream passing through the glottis takes up the vibrations of the cords and, according to the shape and size of the air chambers above, one or another group of the partial tones contained in the laryngeal note is magnified by sympathetic resonance, giving rise to the varied vowel sounds characterizing the voice. The property of elastic bodies to magnify sound by sympathetic vibration



Fig. 1.—Male, aged 25. Supposedly normal case; v. Pirquet test negative, but physical examination revealed slight crackling at left apex and rough murmur at right. The negative was taken in the phase of deep inspiration, the effort to inspire being continued with nose and mouth closed. The vessels are markedly injected with blood and the bronchi with air. Note the suspicious area of congestion in the upper, outer half of left lung. The print illustrates the plainly vascular constitution of the normal right hilus. Note also the shadow of the ascending aorta blending with that of the superior vena cava on the right of the mediastinum.

is of fundamental importance in the apprehension of the physical signs of the chest. It seems obvious that the air waves which are excited by tissue vibration can in turn, when powerful enough, react on distant tissue and produce or increase vibrations in it, just as a singing voice calls forth a response from the wires and sounding board of an open

piano. Thus a sound heard on auscultating any part of the chest is primarily due to tissue conduction or air transmission of vibrations arising in the larynx. The quality, pitch and intensity of the sound heard with the stethoscope depend on the acoustic conductivity and sympathetic resonance of the tissues traversed, and especially on the resonating and conducting properties of the tissues immediately under the bell of the stethoscope. Thus, the examiner can usually declare with confidence the situation of a small superficial excavation anywhere in the lungs,

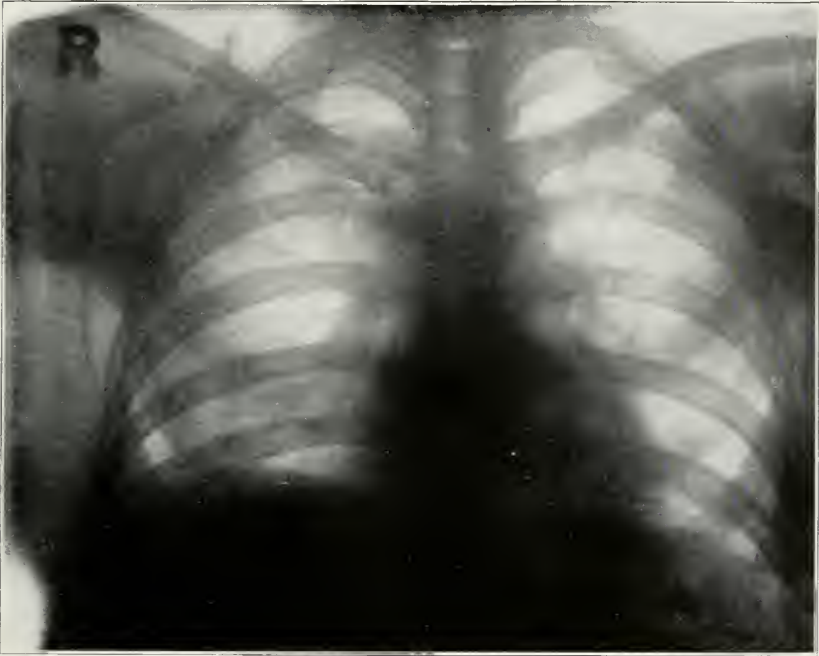


Fig. 2.—Same, supposedly normal, subject as Fig. 1, but the negative was taken in the phase of forced expiration, the effort being continued with nose and mouth closed. Note the diffuse shadow covering both lungs due to crowding together of pulmonary capillaries. Apparently distended bronchi are seen outside each hilus. The larger blood-vessels are compressed and obscured. The sign of abnormal congestion below the left clavicle still persists. The greater congestion of the right apex is of doubtful significance.

presumably because the cavity forms a veritable resonator for the vibrations reaching it. Again, the modification of voice and whisper in a limited section of the lung gives evidence of a local intense congestion or consolidation through which distant vibrations are more readily transmitted to the surface. The examiner who listens to the sounds in the chest inevitably tends to ascribe to the visceral conditions on which his mind is fixed all the auditory phenomena that are manifest. Neverthe-

less, there is a constant source of error, often of considerable magnitude, in the interpretation of thoracic sounds. This consists in the sympathetic vibration of the chest wall itself, due to phonation, and which in its more exaggerated form appeals to the sense of touch as the "tactile fremitus."

THE ACOUSTICS OF THE NORMAL CHEST

In order intelligently to use the voice and whisper as instruments for the diagnosis of disease the medical examiner must thoroughly apprehend the normal acoustics of the chest. The thorax is a resonator which



Fig. 3.—Female, aged about 28. Early incipient tuberculosis, evidenced by clinical history and physical signs: no sputum. Note the fine, isolated network in the right apex, and the stippling above the left clavicle. There is a somewhat isolated area of congestion on the left extending downward from the first intercostal space, anteriorly (the shadow here is somewhat intensified by that of the breast).

may be sharply differentiated into two parts: first, the viscera enclosed by the chest wall and, second, the chest wall itself. Manifestly, sounds owing their intensity to mural vibrations have very subordinate interest for one who investigates the properties of the underlying viscera; they can but disturb and distract the attention; but by the ordinary mode of auscultation they are inseparable from the visceral vibrations. Fortu-

nately there is an extremely simple and effective method of annulling the sounds intrinsic to the chest wall while leaving unaffected those pertaining to underlying structures. The principles of this method were expounded by one of us many years ago with special reference to the sounds of the heart.¹ If auscultation be performed with the ordinary binaural stethoscope, whose chest- and ear-pieces are connected by plain rubber tubes, and which therefore transmits by pure air conduction, and the bell of the instrument is laid very gently on the skin, there is brought to the ear the combined resonance of parietes and viscera. Let now the bell of the instrument be pressed very firmly against the chest wall and



Fig. 4.—Female, aged 30. Patient well, clinically, and not aware of her condition. Has improved greatly in past six months after very slow convalescence from "typhoid fever." She has well-marked, probably healed, tuberculosis of left apex extending to second rib in front and nearly completely isolated from radiations. A similar condition is seen on the right under the first rib anteriorly. There is a general increased vascularity of right lung dissociated from radiations, with scattered opacities which probably represent altered lymph-nodes.

sound due to sympathetic vibration in the latter is completely blotted out and the attention may be fixed unconfused on the acoustics of the underlying viscera whose alterations alone are of clinical importance. The

1. Sewall, H.: On the Use of Stethoscopic Pressure in Physical Examination of the Heart. *New York Med. Jour.*, 1897, lvi.

reader must test this maneuver at the *base* of a normal chest during vocalization to be impressed with the predominance of mural vibrations in our estimate of the vocal characters of that region. The more powerful the vocal resonance, as indicated by tactile fremitus, the more astonishing is the damping effect of stethoscopic pressure. In the same manner powerful, echoing resonance heard on gentle contact with the *manubrium sterni* may often be completely annulled by firm pressure through the chest piece; that is, the sternum is a sounding board which has given factitious power to the vibrations from below. When the sound is not thus damped the fact is significant of abnormal underlying conducting media between trachea and breast bone.



Fig. 5.—Male, aged about 36. Arrested tuberculosis. Infiltration at each apex, most marked on right. An isolated tuberculous deposit occurs in outer part of left second intercostal space, anteriorly. The finer fibrillations are thought to represent bronchial fibrosis. Note the group of apparent bronchi, in optical section, just outside root of left lung. Note the comparative dissociation of infiltrated areas from the hilus radiations.

There are two qualitative modifications of the ordinary vocal resonance which deserve specific mention. In the first the sound is of a deep, powerful, drumlike, "resonant," "chest tone." It is accompanied by a good deal of tactile fremitus and is especially developed in healthy, vigorous young men. This resonance belongs almost wholly to the chest

wall and is, especially over the lower parts of the lungs, nearly obliterated by stethoscopic pressure. The second form of resonance has quite a different quality and has been characterized as a "ringing bronchophony." It is suggestive of the tones of a soprano voice in its meddle register.

Its typical characters are developed most strikingly in the chests of young females. In our opinion the apprehension of this form of bronchophony is of extraordinary diagnostic importance because it is due not so much to parietal as to visceral vibration, for often it is well-nigh undiminished by stethoscopic pressure; on the contrary, in the conditions noted below, pressure with the stethoscope is apt to render plainer and *bring nearer the ear* the ringing bronchophony; especially is this the case

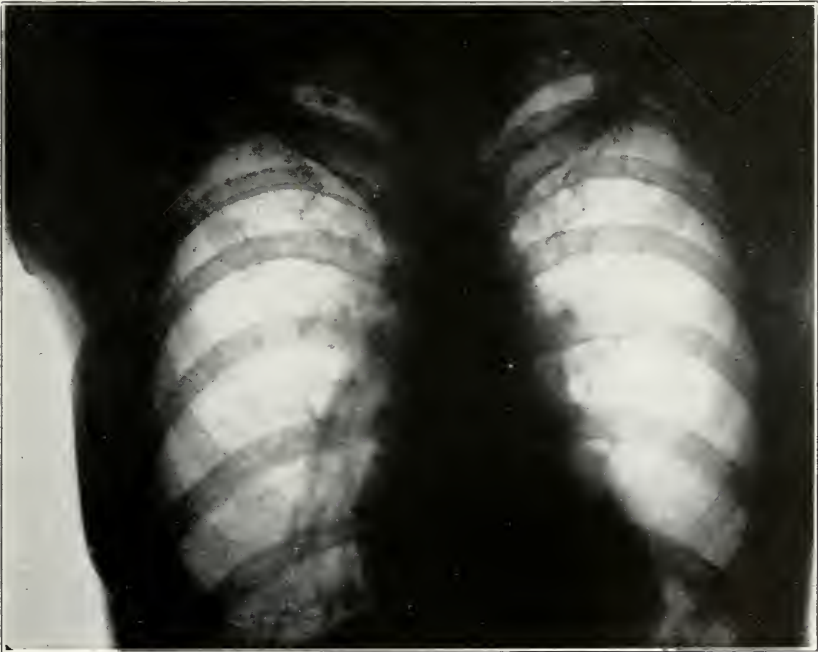


Fig. 6.—Female, aged about 38. Healed or arrested tuberculosis. Note the relatively isolated foci of infiltration and tissue change in and about the apices. Many calcified nodes are scattered through the right lung, and dense streaks of morbid tissue in the upper left. The isolation of the infiltrated areas under the outer ends of the clavicles is marked. The base of the right lung is abnormally congested and is probably seen through thickened pleura.

over the upper half of the lungs. Moreover, the ringing bronchophony is, according to the results of the present investigation, the very earliest sign of a pulmonary change of fundamental importance, namely, vascular congestion, which is possibly combined with a degree of atelectasis. Time and again in this investigation the diagnosis of abnormal vascular con-

gestion has been made as to the lungs of clinically healthy subjects and has been verified by the completely independent interpretation of the x-ray picture of the chest.

Deferring for the present further discussion of vocal resonance in the normal and clinically normal chest, let us consider the acoustic significance of transmitted whisper.

It is a matter of elementary knowledge that whispered sounds have a very restricted distribution through the normal chest and that their extension or change in quality and intensity is one of the surest indications of a pathologic condition. It is here maintained that the special



Fig. 7.—Male, aged 37. Nearly arrested, advanced tuberculosis of both upper lobes, especially on the right. Lungs congested; pleura probably thickened. Marked isolation of affected areas from hilus radiations, especially on the left.

importance of the auscultated whisper is that its transmission is a result of purely visceral conduction and resonance. Mural vibrations usually take no part in the sound. There are two obvious explanations for this fact: first, the relatively low intensity of whispered sound; second, whisper is *noise* due to non-periodic vibrations; sympathetic resonance is fundamentally dependent on periodic vibrations such as make up musical tones. Therefore, except in very few special cases, pressure with the stethoscope does not annul the whispered sound; on the contrary,

this is thereby made clearer and brought, as it were, nearer the ear, probably by reason of the damping of associated adventitious parietal vibrations.

Numerous abnormalities within the thorax modify the intensity, quality and transmission of whispered sound, but one of the most interesting and important is the condition of what is probably intense, acute pulmonary congestion such as precedes actual consolidation of the lung. During the prevalence of influenza in the past winter one of us has had many opportunities of tracing the erratic course of vascular congestion reactive to the infection. These areas of abnormal vascularization show a sharply limited transmitted whisper; in a more advanced stage there may be added an audible expiratory murmur of elevated pitch, and both may pass away without the onset of percussion dullness, etc., indicative of actual consolidation. Skiagrams of the chest in appropriate cases show the negatives to be covered with a more or less dense mist in the regions of transmitted whisper. We are inclined to believe, as illustrated in Figure 2, that the shadow is due to crowding together of the pulmonary capillaries as well as to the relatively diminished volume of the air-cells. This abnormal transmission of whisper in acute disorders indicates a stage of vascular congestion somewhat more advanced than that which may be detected through the "ringing bronchophony." The two signs may occur together or the latter may be found alone. That the increased conductivity which exaggerates the whisper is due rather to congestion than to atelectasis in the lung tissue is indicated by the fact that whispered sound is more intense to auscultation when produced in the phase of extreme inspiration than in that of extreme expiration. Sewall has not been able to detect the abnormally transmitted whisper in cases of simple bronchitis and therefore ventures the suggestion, only, that we have in its occurrence a specific means of distinguishing between congestion of the pulmonary vessels from the right side of the heart and of the bronchial vessels from the left side.

TOPOGRAPHIC DISTRIBUTION OF VOICE AND WHISPER THROUGH THE NORMAL CHEST

It was suggested by Goldscheider² and made very clear by Fetterolf³ that the sounds auscultated at the apices of the lungs were, for the most part, transmitted transversely directly from the trachea. The normal auscultatory differences between the apices is attributed by Fetterolf to

2. Goldscheider: Ueber die physikalische Frühdiagnose der Lungenschwindsucht. *Ztschr. f. klin. Med.*, 1909, lxi, 205.

3. Fetterolf, George: The Anatomic Explanation of the Greater Amount of Vocal Fremitus and Vocal Resonance Normally Found at the Apex of the Right Lung. *THE ARCHIVES OF INT. MED.*, 1909, iii, 23.

the peculiar anatomical relations of the two apices to the trachea. This air tube lies in direct contact with the inner wall of the right apex, while it is separated from the left apex by a considerable thickness of indifferent tissue. The view that apical vibrations were due to direct conduction from the trachea had been reached independently by one of us and has been carried out to its legitimate consequences with interesting results. There is a natural acoustic topographic division of the lungs into two parts, an upper and a lower, according to their relations to the trachea and two main bronchi. The upper parts of the lungs receive, particularly on the right side, vibrations directly from the walls of the great air vessels, so that the intensity of conducted sound as well as the vigor of sympathetic vibration is greatly enhanced in the corresponding region of the chest. This natural acoustic division in the lungs is not striking with the ordinary method of auscultation but becomes very obvious when the principle of stethoscope pressure is applied. Listening over the lower parts of the normal lungs, the resonance, no matter how powerful, is almost completely abolished by firm pressure on the stethoscope. As the instrument explores the front of the chest upward the same result is developed by pressure until it reaches, on the right side, approximately the top of the fourth rib or, on the left, the bottom of the third rib; then quite suddenly the voice sounds persist in great measure no matter what the degree of stethoscopic pressure. The result is easily explained by admitting that the "bronchophony" of the lungs below the fourth ribs in front is almost wholly the sound produced by sympathetic resonance of the chest wall itself. The persistence of voice sound with pressure in the upper chest is obviously dependent not on mural resonance but on direct conduction of vibrations from the contiguous trachea and bronchi. Practically the same acoustic differentiation can be made on the posterior chest wall. The dividing line between upper and lower divisions runs across the back at a point somewhat below the inner ends of the spines of the scapulae—in a situation nearest the roots of the lungs. The acoustic topography in the back is not so sharply defined as in front, by reason of the influence of the large descending bronchial branches, the direct vibrations from which are apt to reach the chest wall as low down as the angles of the scapulae. The examiner will find, of course, that normally all sounds in the upper chest have greatest intensity near the middle line and become weaker toward the lateral margins. It may be mentioned as an extraneous matter that the respiratory murmur itself is intimately related to the parietal resonance of the chest, but this phase of the subject has not yet been definitely investigated.

THE METHOD OF PHYSICAL EXAMINATION

The patient was examined sitting with chest bare by one of us employing the ordinary methods, inspection, palpation, etc., winding up

with a detailed study of the distribution, intensity, quality and prolongation or echoing characters of voice and whisper. All results were definitely recorded in writing. The subject was then *x*-rayed by the other of us, who dictated a detailed description of the plate, summing up with a diagnosis based on the skiagram. The two descriptions and diagnoses were then compared. In the auscultation the subject was asked to pronounce, first by voice and later by whisper, the syllables "one, two, three," and particular attention was paid to the prolongation of the sound from one syllable to the other and to its alteration in quality. No better illustration of the acoustics of the diseased lung can be offered than in the sounds which may be heard in every normal person when the bell of the stethoscope is applied to the back of the neck, high up, or even to the posterior part of the skull. The tones heard here are prolonged, echoing and altered in quality to a degree which is but faintly imitated in the early stages of tuberculosis of the lungs.

In the normal subject bronchial resonance, more or less persisting under stethoscopic pressure, is noted in front, on the right to about the fourth rib, on the left to about the third rib. The whisper, if gentle, reaches on the right scarcely below the first intercostal space and on the left is confined to the inner half of the same. The persistence of the whisper down along the borders of the sternum is suspicious of disease, and isolated areas of prolonged or intensified voice or whisper are certain evidence of physical abnormalities in the chest. As said before, whispered sound is retained during stethoscopic pressure except over the sternum, when this acts as a sounding board. Posteriorly, the acoustic phenomena of the regions above and included between the scapular spines differentiate these parts from those below. On the right vocal resonance is more or less marked throughout the region, gradually fading laterally and below. An echoing character to the sound, especially in an isolated area, and if retained and made more distinct with pressure, is most significant of pathological change.

The whisper should be confined to about the inner half of the right apex; if widely diffused, concentrated in an isolated area or prolonged, it is significant of pulmonary infiltration. On the left the bronchophony is higher pitched and less intense and is apt to reach not so low as on the right. The whisper on the left is normally confined to the upper inner corner of the apex.

It must be granted that the study of the chest according to this method presupposes on the part of the examiner a clear mental picture of the normal acoustic ranges, but a similar qualification is demanded of the expert in every field of physical diagnosis. In Sewall's experience this method of *acoustic diagnosis* is much easier to carry out and more certain in its results than the light "finger-finger" percussion employed

with such success by Goldscheider² in detecting apical changes. The method also is applicable over all parts of the chest and is not limited, like the latter, to the upper portion. Knowing the normal acoustic characters of the apices, it requires but little time or effort to apprehend the signs of disease. A bronchophony ever so slightly metallic and echoing, rendered more distinct and nearer the ear by pressure, denotes a pathological condition in the lung. A whisper distributed unduly widely, especially if prolonged, signifies the same thing. The discrimination of the nature of the pathologic change into congestion, consolidation, excavation, etc., is a matter of detail which does not concern us here.

DIAGNOSIS BY MEANS OF X-RAYS

All examinations were made skiagraphically with the subject stripped to the waist and lying prone with the scapulae thrown well outward. The antikathode was centered over the spine of the fifth dorsal vertebra (opposite the junction of the second rib with the sternum) and at a distance of 25 inches from the plate. The earlier pictures were made with the use of a coil and exposures of five to ten seconds; the later with a transformer and exposures of one-half to two seconds. The later plates were much the more satisfactory.

As it was our special object to determine the skiagraphic signs of the earliest stages of pulmonary tuberculosis and to compare them with the results of physical examination, three classes of subjects engaged our particular attention: (1) completely normal; (2) those suspected of incipient tuberculosis; (3) those certainly afflicted with tuberculosis but presenting doubtful morbid signs to ordinary physical examination. Plates from such cases were compared with those from a considerable series of subjects with more or less advanced tuberculous infection as well as with various chronic non-tuberculous affections of the chest. Our conclusions are founded on the study of 101 cases varying in age from 5 to 59 years; fifty males and fifty-one females. Besides there were considered a considerable number of plates the originals of which were not submitted to physical examination. The extensive literature on thoracic skiagraphy has not yielded to us a wholly satisfactory description of the normal chest negative. In fact, we have come to conclude that the "normal" chest, from the *x*-ray viewpoint, is, at least in the adult, well-nigh an ideal. A person may be clinically perfectly well while the röntgenogram of his chest shows structural changes of pathologic nature. This should be anticipated when we consider that the *x*-ray plate reveals the optically indelible marks of every pathologic struggle which the thoracic viscera have survived. It seems to be the general opinion of investigators that the ordinary contents of the thorax are more or less opaque to the *x*-rays somewhat in the following order: (1) deposits of

lime, as in calcified glands; (2) bone; (3) altered lymph-nodes; (4) blood; (5) fibrous tissue; (6) muscular tissue. It is generally agreed that normal lymph-nodes and early tubercles cast no shadow. The same may be said of mucoid secretions which may give rise to abundant râles.

THE NEGATIVE PLATE OF THE NORMAL CHEST

It is an obvious but important consideration that the technical preparation of the negative largely determines the configurations which it will reveal. In order to distinguish between the dense shadows of the mediastinum, for example, the finer lines in the body of the lung are washed away. The technical skill of the röntgenologist is determined by his choice and use of apparatus best designed to differentiate coarse structures while preserving the details of delicate figures. It is also obvious that the sharpness of outline and apparent density of objects which cast shadows are increased in proportion to their proximity to the plate. Thus a calcified area in a costal cartilage casts a dense and well-defined shadow when the subject lies prone on the plate while the same object may be ill-defined and hazy if the subject lies on his back. Therefore pictures of the same lungs may show very different details of structure, especially in diseased conditions, according as the plate has been exposed at the front or back of the chest.

In the more or less uniformly dense shadow of the normal mediastinum three distinct intensifications of the opacity can be brought out. The topmost obviously is caused by the arch of the aorta which toward its descent is seen in optical section. The middle one, situated within the base of the heart, we believe to be due chiefly to optical section of the pulmonary artery. The lowermost shadow seems to be seated on the diaphragm, and its causation is more problematical. The lateral borders of the mediastinum vary greatly in definiteness, especially on the right side. When the outlines are clear cut, which is especially true in cases of disease in which the mediastinum is broadened, it appears as if the boundaries of the region must be made by the dense, fat-infiltrated, median pleuropericardial membranes seen in optical section. The extreme upper left hand corner of the mediastinum is sharply outlined by a dense shadow which obviously represents the arch of the aorta and projects as a more or less prominent circular segment which has no doubt frequently been misinterpreted as an aneurysmal dilatation. The left outline of the descending aorta inclines inward from the arch and is usually lost in the shadow of the spine at about the level of the seventh dorsal vertebra. In a few pictures, mostly when taken in extreme inspiration, the outlines of the ascending aorta may be traced rising from the base of the heart and passing up outside the right border of the vertebral column (Fig. 1); but usually this part of the aortic arch is hidden within the shadow of the

spine. With the antikathode situated as described the summit of the aortic arch should about correspond with the lower edge of the sternal attachment of the clavicles. A constant veil-like, or sometimes rather dense, shadow forms a strip some two-thirds of an inch in width and extends, tangent to the spine, from the inner, lower border of the right clavicle to the superior outline of the right side of the heart in which it terminates after apparently bending somewhat inward. This shadow is usually, and probably correctly, ascribed to the superior vena cava. It may be intensified by the shadows of the ascending aorta and the root of the right lung. The shadow of the heart does not particularly concern us here and the special consideration of its extraordinary variations is reserved for another communication.

The trachea is readily recognized as a dark streak half an inch or more wide with whitish edges, running down the upper spine more or less to the right of the median line and usually inclining decidedly to the right after entering the thorax. The main right bronchus is clearly distinguished leaving the trachea at a very oblique angle; it enters the root of the lung from its mesial side and frequently radial dark streaks, lesser bronchi, spring from its extremity within the hilus and reach to the diaphragm and far toward the outer confines of the lung. Surrounding the main right bronchus, chiefly on its outer border, is one of the most characteristic, variable and important skiagraphic features of the chest. It is the shadow of the hilus or root of the right lung. Its outer margin usually reaches about $1\frac{1}{2}$ inches to the right of the spine and its upper and lower borders are commonly included between the lower margin of the sixth and the upper margin of the eighth ribs posteriorly. But variations in the area and the structural characters of the root form perhaps the most striking features of early pathological changes in the lung. Between the bronchus and the vertebral shadow the root is usually represented on the negative as a more or less dense, homogeneous cloud, though in development of the plate this space may be cleared so that the portion of the root inclosing and external to the bronchus may be separated from the mediastinal shadow by a dark band. The root external to the bronchus varies indefinitely in its structure. In the normal subject it resembles somewhat a semitransparent cirrus cloud which may be homogeneous or crossed with more opaque streaks or mottled with denser nodules, and it is interspersed with dark areas which evidently represent longitudinal or optical sections of the bronchial branches. In the more successful negatives well-outlined, homogeneous shadows run through the root and can hardly be anything but the larger blood-vessels (Fig. 1).

Of all our negatives perhaps the most instructive were those taken from two subjects, both young men, of 25 and 29 years, respectively, one of whom was in all respects normal and the other presented to physical

examination slight suspicion of apical infiltration. Negatives were made of these subjects in various phases of respiration. In forced expiration, in which the expiratory effort was continued with the nostrils pinched together at the end of deep expiration, the general field of the lung was shadowed, evidently by the crowding together of the minute blood-vessels as well as by compression of the air-cells; the apices were brought well into view by depression of the clavicles and their vessels were injected (Fig. 2). Especially interesting were the pictures taken at the end of deep inspiration, the inspiratory effort being continued with nose and mouth closed for several seconds before exposure. In these negatives the ramifications of the vascular tree were well-defined throughout the lungs, and at the same time the divisions of the bronchial air-tubes were clearly indicated. The root of the right lung in one of the pictures (Fig. 1) was manifestly made up of a great vascular trunk from which clearly defined branches could be traced, breaking into finer and finer divisions, to the outskirts of the lung. On most plates the root area is coarsely mottled with more or less diffuse opacities varying from one-eighth to one-third inch in diameter, and in cases of tuberculous disease, or of older "normal" subjects, very dense circular or irregular shadows, usually not exceeding one-fourth inch in diameter, may be scattered through the roots.

The radiographer is apt confidently to define these denser concretions as calcified glands, and such they probably are. In a negative taken during deep inspiration we found a cluster of four tiny very dense nodules typical of calcification. In two other plates from the same subject, one taken in deep expiration and the other in moderate inspiration, the same nodules were recognized but appeared diffuse as do the shadows of small blood-vessels. The interpretation of less dense and more diffuse opacities is chiefly guess-work. They usually represent either pathological lymph-nodes or blood-vessels in more or less optical section. The beginner in such diagnoses is apt to class them all as bronchial glands but with riper experience he is almost equally inclined to consider them to represent blood-vessels seen in optical section. For our part we think that the homogeneity of the nodular shadow, with a density decreasing from the center, stands for its vascular origin, while internal differentiation or irregularity of outline of a markedly dense shadow signifies glandular infiltration; each case must be judged by itself.

The main left bronchus, less often seen than the right, takes a course more nearly horizontal than the latter. The hilus shadow which surrounds it is therefore somewhat elevated and displaced to the left. The root of the left lung is apt to be obscured by what we take to be the pleuro-pericardial membrane which forms the left border of the mediastinum. It is usually more homogeneously cloudy and less clearly differ-

entiated in structure than the right root, probably because of its closer contact with the pulsatile structures of the mediastinum. Just outside the lower border of this root it is common to find opaque, diffuse masses of probably vascular origin and these are habitually interspersed with four or five well-defined, dark, circular or elongated areas which undoubtedly represent the sections of a cluster of bronchi, since they persist in plates of the same chest taken in states of extreme inspiration and forced expiration. Furthermore, as the physical examination at times determines a well-marked isolated echo of voice and whisper in the nearest area on the front of the left chest, between the third and fourth left costal cartilages, it may be assumed that such bronchi occasionally incline forward from the root. Less constantly, in our plates, in a similar area in the right lung, that is, outside the lower margin of the root, a group of circular shadows, apparently bronchi, can likewise be made out. In certain degrees of pulmonary fibrosis the circular dark areas, which we interpret as optical sections of bronchi, are numerous and widely distributed through the lungs. Radiating from the roots of the lungs are the branches of the "bronchial tree." We have been accustomed to group them as lower vertical, lower oblique, lateral, upper oblique and upper vertical; the oblique being usually offshoots from the vertical radiations. Seldom have we found the well-marked differentiation of three main stems on the right as distinguished from two on the left as described by Dunham and his coworkers.⁴ The radiations on the left, especially in the lower part of the lung, have a diffuseness and homogeneity which distinguishes them from the sharply defined figures on the right, although some of our plates show them equally as clear-cut. Dunham's explanation of this difference as being due to the greater influence of cardiac pulsation on the left side can hardly be questioned. The radiations proceed from the root, branching into finer and finer offshoots forming a tangled network which in the best negatives is visible to the extreme confines of the chest. The vertical, ascending and descending, are usually much more prominent than the lateral radiations. Circumscribed within the radiations are circular dots of considerable opacity which manifestly, in many cases at least, represent the optical sections of vascular offshoots from the parent blood-vessel. We do not enter the still vigorous debate as to the anatomical origin of the so-called "bronchial tree," but maintain that in the negative of the normal lung of the youthful subject the opaque radial shadows are wholly, or nearly wholly, of blood-vascular origin, while the dark streaks represent ramifying bronchi. A structural mark of the hemic origin of a radial shadow seems to us to consist in the homogeneity of the shadow.

4. Dunham, Boardman and Wolman: The Stereoscopic X-ray Examinations of the Chest with Especial Reference to the Diagnosis of Pulmonary Tuberculosis. *Bull. Johns Hopkins Hosp.*, July, 1911, 229.

In older subjects and in lungs altered by disease it is common to find sharply double-contoured radiations inclosing an unshadowed core; these are probably bronchi. In such radiations especially dense and often irregular concretions are numerous and have been defined by us as fibroid or calcareous glands. Little doubt can exist that an especially dense shadow occurring isolated in a dark field and of greater diameter than the radiations about it is even in the "normal" subject due to a glandular concretion. Radiographic study of the apices of the lungs, so important in considering the early changes in tuberculosis, should engage a special arrangement of plate and table. In our work, a uniform, faintly "ground glass" appearance of the apices was presumed to be normal. It is common to find the internal half of each apex traversed by delicate fibrils which are continuations of the vertical radiations from the root, and the whole field may be softly stippled with what are evidently vascular nodules. A fine network of what we interpret as vascular lines is sometimes seen throughout the field of the apex in young subjects (Fig. 3). This appearance is probably typical of incipient apical tuberculosis; it is probably preceded by the stippled condition referred to above. The configurations in the apex closely resemble those, undoubtedly of vascular origin, which appear in the inferior lappets of the expanded lung where it fills in the space made by retreat of the diaphragm from the chest wall. (Fig. 1.) The lower half of the left lung is usually deficient in the network configuration conspicuous on the right side, possibly because the vertical elements of the arborization are blurred by the pulsations of the heart. Not infrequently large unshadowed areas or clefts may appear on a plate showing otherwise good general detail of configurations. They are doubtless due to the fact that, especially in the phase of inspiration, certain sagittal sections of the lung are relatively free from opaque structures.

As an interesting side issue, attention may be called to the extraordinary lateral compression of the liver which results from vigorous inspiratory contraction of the diaphragm. Such massage must be of extraordinary moment to the circulation (Figs. 1 and 2).

To conclude this description of the normal lung-negative, we think that the configurations in the skiagram of the lungs of a youth free from history of chest disease are almost altogether of vascular origin. Nevertheless, in the neighborhood of the hilus a bronchus seen in optical section may occasionally have its circumference indicated by a definite ring (as in the right hilus in Fig. 1). As age increases, especially in subjects who have habitually breathed in a dusty atmosphere, the roots and radiations of the lungs exhibit concretions and intensified streaks which at present are interpreted by us as resulting from deposits in the bronchial glands and from peribronchial fibrosis. In the healthy lung all collections of dense shadows are in immediate relation with the root.

THE SKIAGRAM OF THE TUBERCULOUS LUNG

In the advanced case of tuberculosis the picture differs so widely from the normal as to appear to be characteristic of the disease; yet we have not been able to distinguish in the *x*-ray plates such cases from that of a patient who succumbed to a lung disease of undetermined nature in which sputum examination remained for years negative as to tubercle bacilli. A presumably non-tuberculous stone-cutter furnished a skiagram in which except for the relatively moderate involvement of the apices, the mineral deposits occasioned opacities resembling the densest of tuberculous structures. The negative of the lung in advanced tuberculosis shows usually most marked changes at the apices and upper lobes. More or less dense masses of shadow occur throughout the affected portion. A very characteristic appearance is the loss or diminution of radiations between such shadows and the root of the lung, and a separation of the shadowed areas from the general scheme of arborization. It is to be suspected that the *x*-ray diagnosis of early incipient cases of tuberculosis has usually been attempted from the viewpoint of this morbid picture rather than from that of the normal one.

Before attempting to designate the Roentgenographic criteria of incipient tuberculosis it will be profitable to consider from an *a priori* standpoint what changes the skiagram in such a condition should be expected to show. It is generally admitted that fresh, newly-formed tubercles cast no shadows in the radiographs. Max Cohn,⁵ who has devoted special study to the subject, declares that the characteristic mottling found on the negatives in cases of acute miliary tuberculosis is due, not to the tubercles themselves, but arises from the intense vascular engorgement accompanying the condition. A case of our own has impressed us with the correctness of this conclusion. We can set no limit to the interval between the formation of the tubercle and the development within it and in the surrounding tissues of such physical changes as will block the *x*-rays and cast a shadow. It may well be that in tuberculous tissue opacity to the rays may be long delayed after the advent of clinical tuberculosis, which is essentially a chemical-physiological phenomenon.

If the Roentgen-rays then, are to aid in the early diagnosis of pulmonary tuberculosis, it must be chiefly or largely through their ability to differentiate vascularities in the lungs. In their excellent paper Dunham⁴ and his co-workers think they have distinguished a pathognomonic sign of early tuberculous infections in the delicate arborization of fine lines frequently seen in the negatives from cases of incipient tuberculosis. If we have rightly apprehended their description we must ascribe this

5. Cohn, M.: Die anatomische Bedeutung der Lungenröntgenogramme und ihre Beziehungen zur Röntgendiagnostik der Lungentuberkulose. *Ztschr. f. Tuberk.*, April, 1911, xvii, 217.

configuration to a vascular engorgement which cannot, strictly speaking, be considered of itself alone as pathognomonic of tuberculosis. If changes in vascular congestion connote the incipient stage of tuberculous infiltration, their recognition must be determined by comparison with the normal circulation pictures. We shall return to this subject later.

The apex of the normal lung has usually appeared on our negatives as a uniformly unshadowed or slightly "ground glass" field without configurations. But it is common to find linear extensions of the vertical radiations from the root penetrating and traversing the inner portion of the apex, especially on the right side. These are usually taken for normal figures; nevertheless it is well to bear in mind the careful work of F. W. Jones,⁶ who advances the hypothesis that infection of the right apex arises from direct contact with the main right trunk of the thoracic duct in which the tuberculous process starts. The local changes in such a process should be impressed on the negative. Occasionally, and especially in undoubted cases of tuberculosis, the linear streaks are not confined to the inner part of the apex, but this whole region is occupied by a network of similar fine lines running in all directions; more commonly still, a soft stippling is imparted to the area.

A study of our negatives leads to the conclusion that this appearance of an isolated vascular network in the apices is typical of a condition which, occurring anywhere in the lungs, is indicative of a focus of tuberculous irritation. In the normal lung picture the arborizations are wont to have a characteristic regularity. The size of the trunks diminishes regularly from their origin at the hilus and their branches break up into finer and finer twigs which interlace, more conspicuously in the right lung, and the network becomes more delicate until lost in the periphery. Such a regularity of arborization is still maintained in the greatly intensified configurations presented in non-tuberculous patients having symptoms of chronic bronchitis with asthma and in whom fibroid changes in the lungs, with more or less pneumonokoniosis are suspected, though we are inclined to think that the discrete masses found in the lungs in cases of "miners' consumption" may likewise occur dissociated from the radial figures. The evidence leads to the suspicion that isolated patches of accentuated vascularity, not directly related to the radial vessels springing from the hilus, are the very earliest pathognomonic skiagraphic signs of tubercularization of the lung tissue.

A still earlier skiagraphic evidence of tuberculosis which, however, does not appear to us to be specific of the disease, is an increase of vascular congestion denoted by thickening of the vessels supplying the affected

6. Jones, F. W.: An Anatomical Inquiry into the Pathway of Tubercular Infection, *Lancet*, April 2, 1910, 914.

areas which themselves are hyperemic. Both Levy-Dorn and Cornet⁷ and Dunham⁴ call attention to the same appearance. This thickening of the main trunk connecting the hilus with the tuberculous area may be noted in an old case of disease in which activity is renewed; but, as pointed out above, we believe the characteristic tuberculous picture tends to preserve the peripheral network while more or less eliminating the radial stem from which it arose. It is as if the infecting seed transported to a peripheral area had there multiplied independently.

It is impossible to determine from the x-ray negative at what period the area of localized congestion, which we think the earliest sign of parenchymal tuberculosis, begins to show the shadows of tuberculous deposits *per se*. In old tuberculous infiltrations one can only surmise, often, which shadows are due to pathological deposits and which to vascular congestions. If these parenchymal vascular changes have any relation to early tuberculous infiltration it must be conceded that they characterize the lower portions of the lung scarcely less than those pertaining to the apices. We shall revert to this point later. But it is the appearance of the hilus regions which especially attracts the eye in the Roentgen negative. Increase in the area of the root shadow, alterations in the apparent consistency of its matrix, nodular condensations which are inevitably referred to glandular changes, are common when the rest of the lung presents nothing abnormal. Hence it is the common view of radiologists that tuberculous infection begins at the root of the lung, while pathologists are generally agreed that, at least in adults, the disorder arises at the apices. We cannot but suspect that both opinions are formed on facts whose antecedents have escaped observation. We may be permitted to express a provisional hypothesis which these x-ray studies have suggested. The suspicion is strong that pulmonary infection usually finds its first seat in the glands at the lung roots. The infection proceeds thence in all directions. But the mechanical conditions at the apex are such that the lung in this region has relatively little power to expel the intruding bacillus which, therefore, is enabled to settle and reproduce its kind.

The instructive experiments of Baemeister⁸ are pertinent in this connection. It is well known that intravenous inoculation of tubercle bacilli may be followed by a general but not especially an apical tuberculosis. Baemeister inoculated a series of rabbits through an ear vein with an emulsion of tubercle bacilli. In some of the rabbits he had previously to an extent constricted off the apices of the lungs by a wire

7. Levy-Dorn, F. M., and Cornet, H.: Das Röntgenbild des normalen Thorax mit Rücksicht auf die Diagnose der Phthisie, Berl. klin. Wchnschr., May 25, 1908, xlv, 1004.

8. Baemeister: Experimentelle Lungenspitzen-tuberkulose. Achtundzwanzigste Kong. f. inn. Med., 1911, p. 290.

twisted about the anterior part of the chest. In these cases isolated, apical lung tuberculosis was produced. Further, the elaborate studies of Hart⁹ showed that persons having a short first rib, by which the apex is constricted at its junction with the lower lung, are distinctly predisposed to tuberculous infection.

X-ray study, in our opinion, gives support not only to a theory of root origin of the infective process, which, according to Rieder¹⁰ and others, is constant, but to the view that in certain cases the apex is the source of the trouble. In the plates from these patients there is well-marked vascularity at the apex and the root itself is practically normal. But separated from and parallel to its outer circumference may be found a crown of well-marked opacities which forms a distinctive picture.

It may be repeated that in the very earliest cases of tuberculosis nothing more distinctive is portrayed than evidence of increased vascularity, which may be noted in one or both bases as well as in the apices, and in which areas of congestion tend to occur like nests more or less distinct from the hilus radiations.

These features become more and more pronounced, with the addition of signs of tissue changes, as the clinical course of the disease progresses.

The reaction to tuberculin injections, as investigated in numerous German researches,¹¹ would seem to offer crucial evidence of the pathological significance of the skiagraphic changes. This, however, is a false hope, for after a positive tuberculin test we are still in doubt as to whether the reacting focus has been latent or of clinical significance. It was considered inexpedient to submit our patients to the subcutaneous test, but the v. Pirquet skin test was made in forty-seven cases. Of these forty-one reacted positively, two of them only after a second trial, and six negatively. In the forty-one cases with positive reaction the physical diagnosis of the lungs was negative ten and doubtful fourteen times; the x-ray diagnosis was negative thirteen and doubtful fifteen times. In two patients, aged 19 and 20 years, the skin test was in each twice negative, while the physical and x-ray findings were positive. In two other patients, aged 50 and 25 years, negative to v. Pirquet, our examinations were classed as doubtful. It is probable that with wider experience the length of our "doubtful" list would be considerably reduced. This investigation has proved so full of suggestion that we regard the careful study of 100 subjects only as the introduction to further research. We

9. Hart, Carl: Die Disposition der Lungenspitzen zur tuberkulösen Phthisie und das Lokalisationsgesetz des ersten Tuberkulösenherdes. München. med. Wehnschr., Jan. 19, 1909, lvi p. 123.

10. Rieder, H.: Die frühzeitige Erkennung der Lungentuberkulose mit Hilfe der Röntgenshatten. Deutsch. Arch. f. klin. med., 1909, xciv, 62.

11. Cf. researches by Schlayer, Deutsch. med. Wehnschr., 1908, xxxiv, 866; Max Wolff, Berl. klin. Wehnschr., Jan. 17, 1910, xlvii, p. 118 (Abst.), etc., etc.

have found a general, and frequently surprisingly close, agreement between the conclusions arrived at through physical examination and study of the *x*-ray negative. Though the interpretation of the meaning of morbid physical signs was frequently in error, such signs when found were demonstrated almost invariably on the *x*-ray plate to have a physical basis.

SUMMARY

Our general conclusions may be summarized as follows:

1. Auscultation of the voice and whisper affords an exceedingly delicate index of pathological changes in the lungs.

2. Vocal resonance involves vibrations both of the thoracic viscera and of the chest wall. The latter vibrations may be damped and removed from consideration by pressure applied to the bell of the simplest form of air-conducting stethoscope. The whisper, under ordinary conditions, does not evoke the resonance of the parietes; it bespeaks only visceral conditions. It is rendered plainer and brought nearer the ear by stethoscopic pressure.

3. For the purposes of physical examination the lungs are separable into two natural divisions, namely, the parts above, which receive directly the transverse vibrations emanating from the trachea and larger bronchi; and the parts below, inferior to the third intercostal space in front, which are relatively removed from their influence.

4. With our present ability to produce and interpret *x*-ray pictures, it must be admitted that a judgment founded on clinical history combined with physical signs may lead to a strong suspicion of tuberculous infection long before any signs of actual tissue changes, except those involving the bronchial glands, appear on the *x*-ray negative. Nevertheless we believe that a skiagram of the chest, preferably repeated at not infrequent intervals, is essential to the proper understanding of a patient's condition.

5. Skiagraphic study of the chest resolves itself into two natural divisions; one pertains to the hilus regions, concerning especially the bronchial glands, with their associated peripheral lymphatic nodes, and the other includes the parenchyma of the lungs itself.

6. Extreme pathological changes in the glands may be recognized with great facility, but alterations of moderate grade need careful judgment in their interpretation.

7. We agree in the view that in the *x*-ray negative of the normal chest the opaque arborizations of the "bronchial tree" are almost wholly composed of shadows cast by blood-vessels. In non-infected subjects the bronchial tree has a typical symmetry and regularity of distribution. It is very suggestive of the shadow of a leafless tree cast by the sun on an asphalt pavement.

8. In practically all our cases of unproved but suspected tuberculosis the skiagraphic negatives exhibited more or less extensive areas of pulmonary congestion, denoted by thicker branches and denser arborizations of the "bronchial tree." As pointed out in the text, such congestion may possibly be recognized clinically by a "ringing" quality of the bronchophony which persists under stethoscopic pressure. We are constrained to believe that the recognition of abnormal congestion has great importance in the early diagnosis of pulmonary tuberculosis. Moreover, since Levy-Dorn and Cornet, Dunham and his co-workers and ourselves, have independently recognized a peculiar vascularization of the lungs in association with tuberculosis, it seems probable that herein exists a specific diagnostic property of the *x*-ray plate.

9. We proceed, however, a step further and venture the opinion that in tuberculosis of the lungs the earliest pathognomonic skiagraphic sign is the representation of comparatively isolated areas of vascular congestion, which increase independently of their connections with the central root. This peripheral focalization of the congestive process and its severance from the main system of vascular radiations are apt to become more and more prominent as the disease progresses and shadow-creating deposits are formed.

THE SELECTIVE RELATION OF CERTAIN VITAL STAINS TO THE TUBERCLE*

PAUL A. LEWIS, M.D.

PHILADELPHIA

Certain coloring matters are known which, when administered to the living animal, stain portions of its tissues without destroying the life of the animal or that of the affected tissue. The first scientific use of observations of this order is attributed by Fischel¹ to Misaud (1567), who found that when animals were fed with madder the actively growing portions of the bones were stained red. The long continued researches of Ehrlich on the physiological relationships of the anilin dyes has resulted in many additions to the list of substances exhibiting this form of activity, and it is to be foreseen that much valuable information will in the future be derived from the systematic use of such methods.

Recently Goldman,² in the course of other studies, has applied vital staining methods to a study of tuberculosis as produced by the inoculation of mice. He used isamin-blue for this work. His results, briefly summarized, were, that in the mild disease caused by inoculating mice with avian tubercle bacilli certain wandering cells of the tissues, which have a special affinity for this stain, are very active. In the acute disease caused by the inoculation of virulent bacilli of bovine type, these cells play a much smaller part.

Brown and Evans of Baltimore, in studies so far unpublished, but reported before the American Association of Pathologists and Bacteriologists at Philadelphia, in April, 1912, found that in the rabbit's liver, in the formation of the early tubercle produced by the direct inoculation of this organ, the stellate cells of Kupffer take an active part. The part played by these cells could be most distinctly followed when they were marked out by staining the animal, before inoculation, with trypanblau.

The material at the Phipps Institute has recently afforded us an excellent opportunity to examine by these methods another aspect of the tuberculosis problem. The results have been sufficiently interesting to deserve the following brief description:

*From the Henry Phipps Institute of the University of Pennsylvania.

*Read before the Pathological Society of Philadelphia, June 13, 1912.

1. Fischel: Vital Färbung in Enzyklopädie d. Mikroskopischen Technik, ed. 2, ii, 590.

2. Goldman, E. E.: Die äussere und innere Sekretion des gesunden und kranken Organismus im Lichte der Vitalen Färbung. Beiträge zur Klinischen Chirurgie, March, 1912, lxxviii, No. 1.

When rabbits are inoculated intravenously with a suitable number of tubercle bacilli of human type they survive for months. If such an animal is killed in from two to four months subsequent to inoculation, there are found, very constantly, well-developed tubercles in the lungs and in the kidneys. The lung tubercle is usually located beneath the pleural surface and varies in diameter from 1 to 5 mm. Occasionally larger masses, evidently conglomerations of the smaller, are found. These tubercles in the lungs are largely made up of moderately firm fibrous tissue and are not infrequently caseous at the center. The kidney tubercles are of about the same size, but are less frequently caseous.

Our experiments have made use of such animals and they have been further treated with the dye-stuffs, trypanrot and isaminblau. The following abstracts from the protocols and brief discussion will show the interest attached to the experiments:

I. Isaminblau: Rabbit 371, Feb. 2, 1912, was inoculated intravenously with .5 mg. culture T 2.10 (human type). May 26, 1912, injected intravenously 50 c.c. 1 per cent. isaminblau R. Intraperitoneally 25 c.c. of same. Animal moderately blue at once; increasingly so for several days. June 3, 1912, killed. Autopsy: Scattered tubercles in the lungs and kidneys. The tubercles are stained intensely blue, especially in their outer portions. Microscopic examination of frozen sections shows that the dye appears as granules in large mononuclear cells of the type of endothelial phagocytes. These are found chiefly in the periphery of the tubercular areas. A few are found deep in. Scattered cells of similar type also containing dye-stuff are found along the connective tissue bands of the normal lung tissue. There is in the tubercle a small amount of hyalin substance which takes a very pale blue stain. The tubercles in this animal show very little caseation and this is unstained.

II. Trypanrot.—Rabbit 306, Jan. 9, 1912, was inoculated intravenously with 1 c.c. of suspension of original material of cervical glands C. (Human type infection.) May 27, 1912, injected subcutaneously 10 c.c. of 1 per cent. trypanrot. May 28, 1912, skin and visible membranes moderately red. June 4, 1912, skin and membranes still red. Animal killed. Autopsy: Few scattered tubercles in lungs. None in any other organ. Some of the smaller tubercles in the lung are stained faintly pink. Most of the smaller ones and all of the larger ones are stained a faint pink in their outer portions and are intensely red in an irregular central portion seen only on section. The lung tissue is unstained. Microscopic examination of frozen sections shows a few scattered mononuclear phagocytic cells in the outer portion of the tubercles containing red granules. Many other such cells contain no stain. The centers of the larger tubercles and those of some of the smaller ones are caseous. The caseous material is stained diffusely and quite intensely red.

The first of these experiments shows again the selective action of isaminblau for the large mononuclear phagocytic cell as pointed out by Goldman. These cells are found abundantly in the peripheral portions of fibroid tubercles.

The second experiment is of great interest, showing, as it does conclusively, that extraneous chemical substances of proper constitution

may within a few days penetrate to the caseous center of a tuberculous mass and become concentrated there in greater degree than in the normal surrounding tissues. The particular substance used in this experiment, trypanrot, may probably be without effect on the lesion itself, but the result should be a great stimulus to future work in a similar direction.

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BOOK REVIEW

A CYCLOPEDIA OF AMERICAN BIOGRAPHY, COMPRISING THE LIVES OF EMINENT DECEASED PHYSICIANS AND SURGEONS FROM 1610 TO 1910. By Howard A. Kelly, M.D. Illustrated with portraits, in two volumes. W. B. Saunders Co., Philadelphia, 1912.

We cannot be too thankful to Dr. Kelly for compiling this valuable bibliographical cyclopedia, entailing as it does not only time and patience by those collaborators who have so carefully collected material from various parts of the country, but energy and industry in arranging this material for its two large volumes. The bibliography extends from the year 1610 to 1910 and comprises a short individual account of eminent physicians, surgeons and men of science who lived in America during this period. It is certainly more extensive than any American bibliography which has hitherto been published and includes the lives of many men, long since forgotten by the world at large, but who, it seems, as one reads their short histories, have left a record worthy to be set down in these volumes.

The actual bibliographical notices alphabetically arranged are preceded by a short introduction including sections on the history of Anatomy by Bardeen, of Surgery by Martin B. Tinker, of Gynecology and Obstetrics by Dr. Kelly himself and the special subjects of Dermatology, Ophthalmology, Laryngology and Medical Jurisprudence. There is some lack of proportion in these sections. Nowhere is to be found the history of internal medicine, nor is there any reference to the development of the sciences of pathology and physiology which might have made an interesting chapter. On the other hand the space devoted to laryngology is out of all proportion to that assigned to other and broader subjects. In the preface the author draws attention to the lack of uniformity of style and treatment which must necessarily exist in the individual biographies. This in itself could hardly be considered a mistake, but a fault to which he also draws attention seems a little more unfortunate when men of relative unimportance are given more extended notice than their "worthier compeers." Though this perhaps was unavoidable owing to the great number of contributors, yet it seems as though the introduction might have been more nearly uniform.

The individual histories, often with references attached, in spite of any slight defects, are on the whole most excellent, short, concise accounts; with more extended and complete lives of those on whom we have come to look as the leaders of the art and science of medicine in this country.

Again we must express our thanks to Dr. Kelly for putting this valuable collection of biographies in the hands of the public.

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THE INFLUENCE OF CARBONATED BRINE (NAUHEIM) BATHS ON BLOOD-PRESSURE *

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Last year I read a paper before this Society entitled "A Résumé of the Opinions Upon the Nauheim Treatment of Chronic Disease of the Heart."¹ In the course of that paper I referred to the following statement made by Mackenzie:²

I found that from ten to twenty years ago, when the notion was prevalent that to have a good heart you must have a strong pulse, these baths had a remarkable effect in strengthening the pulse, raising the arterial pressure 20, 30 and 40 mm. Hg. But nowadays, the fashion being to soften a strong pulse, these waters are discovered to have a remarkable effect in lowering the arterial pressure. So remarkable are these waters that it is averred that they can increase the pressure when it is low and lower the pressure when it is high.

Huchard³ quotes a statement by Bosia: "We have read all the works of Schott and in no part of these have we met precise observations, always affirmations, never facts." Huchard agrees with this statement, and protests against similar exaggerations. He refers to several cases of sudden death of patients who had just returned from a course of treatment at Nauheim, which he reported at the Académie de Médecine. He says that he is not an enemy of carbon dioxid baths in suitable cases of cardiac disease, but that he is opposed to the systematic medication of all cardiac patients.

In the paper which I read at this Society in 1911, I said:

The influence of carbonated brine baths on blood-pressure in the human patient, so far as I know, has never been carefully studied. I have a series of observations on this subject under way at present, which I hope to report at some future day. I am able to say, however, that while the majority of patients show a higher pressure at the conclusion of the baths than at their commencement, there are some patients in whom the pressure has been lower at the termination of the series. I am not unmindful of the numerous other influences that would tend to modify the blood-pressure at work in a patient who is taking a course of sanitarium treatment.

*Manuscript submitted for publication May 24, 1912.

¹Read by title at the twenty-ninth annual meeting of the American Climatological Association, Hartford, Conn., June 10 to 13, 1911.

1. Swan: New York Med. Jour., October 7, 1911, xciv, 713.

2. Mackenzie: Diseases of the Heart, ed. 2, 1910.

3. Huchard: Consultations médicales, maladies du coeur, arteriosclerose, 1910.

AUTHOR'S OBSERVATIONS

In the present communication I wish to report the observations made on the blood-pressure in eighty-one patients who were treated with carbonated brine baths.

MATERIAL

The patients who form the basis of this study were under my care while I was Medical Director of the Glen Springs.

In five cases observations were taken either by myself or by one of my associates, before the administration of the bath, immediately after the bath, and after one hour's rest.

In the remainder of the cases observations were made at the beginning of the treatment and at its conclusion.

In twenty-one cases the course of carbonated brine baths was interrupted, for one reason or another, before the completion of the routine number of baths in the series. In several cases the patient found it necessary to leave the institution. In the remainder of the eighty-one cases the complete series of eighteen baths was given.

Fifty of the patients were males and thirty-one were females. Their ages ranged from 19, the youngest, to 77, the oldest; two of the patients were 77 years old.

They were distributed through decennial age periods as follows: Under 20, one; from 20 to 29, six; from 30 to 39, thirteen; from 40 to 49, ten; from 50 to 59, twenty-four; from 60 to 69, seventeen; over 70, ten.

There were sixteen cases of fibroid myocarditis, three of which were complicated by bronchitis; nine cases of parenchymatous myocarditis; eleven cases of dilatation of the heart; five cases of hypertrophy and dilatation of the heart; five cases of mitral regurgitation; five cases of hypertrophy of the heart; four cases of tachycardia; three cases of aortic regurgitation; three cases of convalescence from acute infections; two cases of arteriosclerosis; two cases of neurasthenia; two cases of convalescence from operations; two cases of arthritis deformans, and one case each of mitral obstruction and regurgitation, diabetes mellitus, beginning interstitial nephritis, hypertrophic cirrhosis of the liver, chronic parenchymatous nephritis, mitral regurgitation and aortic regurgitation, fatty heart, hypochondriasis, weak heart, pulmonary emphysema, gastrectasia and nervous dyspepsia.

METHODS

A physical examination was made of each patient at the time he applied for treatment and another physical examination was made, usually, on the day after the completion of the course of baths. The protocols of these examinations record the location of the point of maxi-

imum intensity of the cardiac impulse; the outline of the superficial area of cardiac dulness; the description of adventitious sounds, if any were found; the character of the diastolic sounds; the character of the muscular quality of the systolic sound; the extent of the superficial area of liver dulness; observations of the blood-pressure; and the rate and character of the pulse. Early in the course of the routine examinations I located the borders of cardiac dulness and the point of maximum impulse with relation to the midclavicular line. Later I located these points with reference to the midsternal line, measuring the distance from that line in inches. At the beginning of my routine examinations I made no attempt to record the size of the area of cardiac dulness; later I began to record the transverse diameter of this area in inches; and still later I recorded the oblique diameter of this area in inches. The oblique diameter was measured from the point of junction of the right border with the upper border of cardiac dulness, to the point of maximum impulse.

The blood-pressure observations were all made in the recumbent posture. The cuff was always applied next to the skin of the arm. A Stanton sphygmomanometer was always used. The auscultatory method of determining blood-pressure was always used. The systolic pressure was recorded as the point at which the first tap was heard. The diastolic pressure was recorded as the point at which the tap disappeared.

The details of the method of administering the baths will be found in a paper which I read before the Medical Society of the State of New York in 1911.⁴

In the case of a male patient (Case 1) aged 76 years, who was suffering from fibroid myocarditis, blood-pressure observations were made just before entering the bath tub, immediately after the bath was given, and after one hour's rest in the recumbent posture. The accompanying table (Table 1) gives the details of these observations.

Before the first bath the patient's systolic pressure was 142 mm., before the last bath in the series his systolic pressure was 135 mm., and an hour after the last bath his systolic pressure was 154 mm. The accompanying chart (Chart 1) of the fluctuations of the systolic pressure indicates that the tendency of the pressure during the course of treatment was upward.

The usual train of circumstances in this case was to find that the systolic pressure was higher immediately after the bath than it was before the bath was given, and after the hour's rest to find it lower than it was before the bath was given. This train of events followed in ten instances.

At the sixth bath the systolic pressure was the same after the bath as it was before; an hour after the bath there was a drop of 22 mm.

At the ninth bath the systolic pressure after the treatment was 2 mm. lower than it was before; and one hour after the treatment it was the same as it was immediately after.

4. Swan: New York State Jour. Med., August, 1911, xi, 373.

At the eleventh bath the systolic pressure immediately after the treatment was 5 mm. higher than it was before. After the hour's rest it was 1 mm. higher than it was immediately after the bath.

After the twelfth bath the pressure fell 3 mm. and after the hour's rest it had risen 8 mm. At the fourteenth bath the systolic pressure was 6 mm. higher immediately after than it was before the bath was given. After an hour's rest it was 7 mm. higher than it was immediately after the bath was given. At the eighteenth bath the systolic pressure rose 18 mm. and after an hour's rest it rose 1 mm.

The immediate effect of the bath was to raise the pressure fourteen times, to lower it twice, and no effect was noted once. The observations at the fourth bath were unfortunately missed. The increases of systolic pressure immediately after the baths amounted to 2 mm., 3 mm., 11 mm.,

TABLE 1.—FIBROID MYOCARDITIS. BLOOD-PRESSURE OBSERVATIONS

No. of Bath	B. P. Before Bath				B. P. After Bath				B. P. One Hour After Bath			
	S.*	D.	M.	PP.	S.	D.	M.	PP.	S.	D.	M.	PP.
1	142	85	113.5	57	144	80	112	64	137	85	111	52
2	145	85	115	60	148	85	116.5	63	139	90	114.5	49
3	137	86	111.5	51	148	83	115.5	65	135	90	112.5	45
4†
5	142	90	116	52	158	92	125	66	138	92	115	46
6	145	82	113.5	63	145	85	115	60	123	75	99	48
7	138	78	108	60	154	82	118	72	148	83	115.5	65
8	144	82	113	62	160	83	121.5	77	149	85	117	64
9	157	78	117.5	79	155	84	119.5	71	155	82	118.5	73
10	125	70	97.5	55	148	82	115	66	135	89	107.5	55
11	125	97	111	28	130	77	103.5	53	131	75	103	56
12	140	95	117.5	45	137	95	116	42	145	88	116.5	57
13	130	83	106.5	47	138	78	108	60	†
14	149	92	120.5	57	155	82	118.5	73	162	85	123.5	77
15	150	86	118	64	158	86	122	72	147	91	119	56
16	143	80	111.5	63	165	95	130	70	148	84	116	64
17	134	80	107	54	145	78	111.5	67	142	82	112	60
18	135	80	107.5	55	153	80	116.5	73	154	84	119	70

*S, systolic; D, diastolic; M, mean pressure; PP., pulse-pressure.

†Observations missed.

16 mm., 16 mm., 16 mm., 23 mm., 5 mm., 8 mm., 6 mm., 8 mm., 22 mm., 11 mm. and 18 mm., respectively; an average of 11.7 mm. at each treatment. The decreases of the systolic pressure amounted to 2 mm. after one bath and 3 mm. after the other.

After the hour's rest the systolic pressure was higher in nine instances and lower in seven than it was before the bath was given. The observation one hour after the thirteenth bath was unavoidably missed. The increases of the systolic pressure an hour after the bath amounted to 10 mm., 5 mm., 10 mm., 6 mm., 5 mm., 13 mm., 5 mm., 8 mm., 19 mm., respectively; an average of 9 mm. at each treatment. The decreases of the systolic pressure one hour after each bath amounted to 5 mm., 6 mm., 2 mm., 4 mm., 22 mm., 2 mm., 3 mm., respectively; an average of 6.2 mm. for each treatment.

At the beginning of the course of treatment the patient's pulse-pressure was 57; before the last bath his pulse-pressure was 55; immediately after the bath it was 73; and after an hour's rest it was 70.

The usual train of events in relation to the pulse-pressure was to have a well-marked elevation immediately after the treatment and a depression after the hour's rest. This train of circumstances followed eleven of the treatments. At the sixth bath the pulse-pressure was 3 mm. lower immediately after the treatment and 12 mm. lower after the hour's rest.

At the ninth bath the pulse-pressure was 8 mm. lower immediately after the treatment and after the hour's rest it had increased 2 mm.

At the eleventh bath there was an elevation of pulse-pressure of 25 mm. immediately after the bath, and after the hour's rest there was a further elevation of 3 mm.

After the twelfth bath the pulse-pressure was depressed 3 mm. immediately and there was an elevation of 15 mm. after the hour's rest.

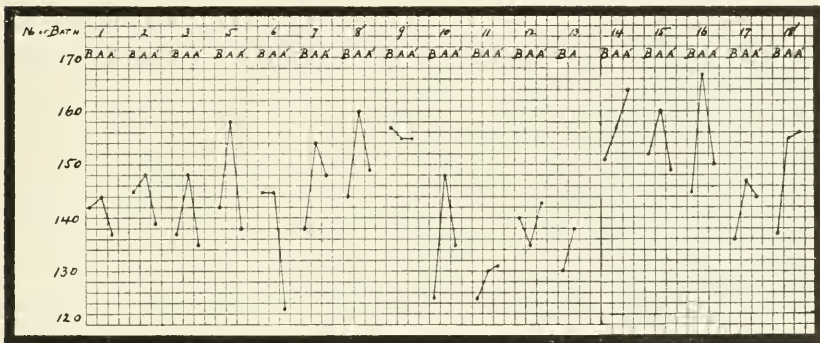


Chart 1.—Systolic blood-pressure curve. Carbonated brine baths. Fibroid myocarditis. B.=Immediately before the bath. A.=Immediately after the bath. A'=One hour after the bath. The observations at the fourth bath and the observation one hour after the thirteenth bath were missed.

Immediately after the bath the pulse-pressure was elevated fourteen times and lowered three times. The elevations amounted to 7 mm., 3 mm., 14 mm., 12 mm., 15 mm., 11 mm., 25 mm., 13 mm., 16 mm., 8 mm., 7 mm., 13 mm., 18 mm., respectively; an average of 12.5 mm. for each treatment. The lowering of the pulse-pressure amounted to 3 mm., 8 mm. and 3 mm., respectively; an average of 4.6 for each treatment.

An hour after the bath the pulse-pressure was elevated eight times; lowered seven times and was unchanged once. The elevations in pulse-pressure amounted to 5 mm., 2 mm., 28 mm., 12 mm., 20 mm., 1 mm., 6 mm. and 15 mm., respectively; an average of 11.1 mm. for each treatment. The depressions of pulse-pressure amounted to 5 mm., 11 mm., 6 mm., 5 mm., 15 mm., 6 mm. and 8 mm., respectively; an average of 8.1 mm. for each treatment.

In this patient the systolic pressure on admission was 142 mm., and during the course of his treatment it increased to 165 mm. on one occasion, and was above 150 mm. on thirteen occasions. The highest increase of systolic pressure at any one treatment was 23 mm.

He had an hypertrophied heart and a fibroid myocarditis. He had a pulse of normal rate, of good strength and volume, and an artery which was recorded as not palpable at the beginning of the treatment and palpable at its close. It may be supposed that in this patient the fibroid changes in the heart-muscle had increased much faster than the thickening of the walls of the peripheral vessels.

The danger of administering a form of treatment capable of producing an elevation of the systolic pressure of 22 and 23 mm., and of 25 to 28 mm. of the pulse-pressure to an individual with thickened and rigid arteries is not, in my opinion, altogether theoretical.

TABLE 2.—PARENCHYMATOUS MYOCARDITIS. BLOOD-PRESSURE OBSERVATIONS

No. of Bath	B. P. Before Bath				B. P. After Bath				B. P. One Hour After Bath			
	S.*	D.	M.	PP.	S.	D.	M.	PP.	S.	D.	M.	PP.
1	107	55	80.5	52	114	55	84.5	59	112	58	85	54
2	114	60	87	54	112	58	85	54	110	58	84	52
3	118	55	86.5	63	112	60	86	52	120	62	91	58
4	107	58	82.5	49	111	62	86.5	49	106	47	76.5	59
5	111	55	83	56	107	64	85.5	43	109	55	82	54
6	114	55	84.5	59	113	58	85.5	55	114	54	84	60
7	110	63	86.5	47	111	68	89.5	43	113	65	89	48
8	112	58	85	54	113	65	89	48	117	70	93.5	47
9	110	52	81	58	110	60	85	50	113	60	86.5	53
0	114	45	79.5	69	115	50	82.5	65	107	48	77.5	59
1	106	53	79.5	53	110	58	84	52	112	55	83.5	57
2	114	54	84	60	117	60	88.5	57	117	57	87	60
3	108	64	86	44	116	70	90	46	114	70	92	44
4	115	75	95	40	120	65	92	55	114	80	97	34
5	109	60	84	49	110	70	90	40	114	83	98	31
6	115	55	85	60	110	60	85	50	115	55	85	60
7	104	57	80.5	47	112	64	88	48	106	65	85.5	41
8	106	64	85	42	113	64	88.5	49	113	64	88.5	49

In the case of a female aged 26 years (Case 16), who was suffering from parenchymatous myocarditis, the observations made before, after, and one hour after the bath are given in Table 2.

In this case there was usually an elevation of systolic pressure (Chart 2) immediately after the bath, and at the end of the hour's rest the systolic pressure was usually higher than it was before the bath was given, although often lower than immediately after the treatment.

Immediately after the bath the systolic pressure was elevated eleven times, reduced six times, and was unchanged once. The elevations of pressure amounted to 7 mm., 4 mm., 1 mm., 1 mm., 4 mm., 3 mm., 8 mm., 5 mm., 1 mm., 8 mm. and 7 mm., respectively; an average of 4.2 mm. for each treatment. The reductions of systolic pressure amounted to

2 mm., 6 mm., 4 mm., 1 mm., 1 mm. and 5 mm., respectively; an average of 3.1 for each treatment.

One hour after the bath the systolic pressure was raised eleven times, reduced five times, and unchanged twice. The elevations amounted to 5 mm., 2 mm., 3 mm., 5 mm., 3 mm., 6 mm., 3 mm., 6 mm., 5 mm., 2 mm. and 7 mm., respectively; an average of 4.2 mm. at each treatment.

The reductions of systolic pressure amounted to 4 mm., 1 mm., 2 mm., 7 mm. and 1 mm., respectively; an average of 3 mm. for each treatment.

The influence on the pulse-pressure in this case was usually a decrease in the pressure immediately after the treatment, followed by an elevation after an hour's rest after half the treatments, and a depression after the other half. The pulse-pressure was 3 mm. lower at the conclusion of the series than it was at the beginning. Immediately after the baths the pulse-pressure was elevated five times, reduced eleven times, and no change was noted twice. The elevations amounted to 7 mm., 2 mm., 15 mm., 1 mm. and 7 mm., respectively; an average elevation of 6.3 mm. after each treatment. The reductions in pressure amounted to 11 mm.,

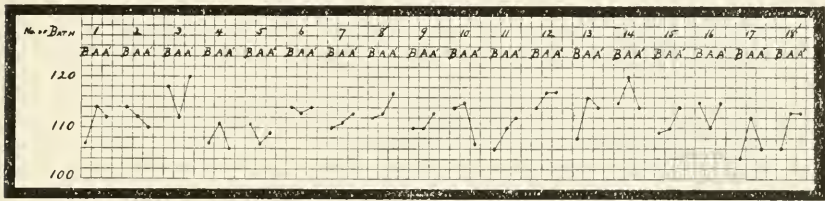


Chart 2.—Systolic blood-pressure curve. Carbonated brine baths. Parenchymatous myocarditis. B. = Immediately before the bath. A. = Immediately after the bath. A' = One hour after the bath.

13 mm., 4 mm., 4 mm., 6 mm., 8 mm., 4 mm., 1 mm., 3 mm., 9 mm. and 10 mm., respectively; an average of 6.6 mm. for each treatment.

After the hour's rest the pulse-pressure was raised six times, lowered nine times, and no change was noted three times. The elevations of the pulse-pressure above that recorded before the bath was given amounted to 2 mm., 10 mm., 1 mm., 1 mm., 4 mm. and 7 mm., respectively; an average elevation of 4.1 mm. at each treatment.

The reductions in pulse-pressure after the hour's rest amounted to 2 mm., 5 mm., 2 mm., 7 mm., 5 mm., 10 mm., 6 mm., 18 mm. and 6 mm., respectively; an average of 6.7 mm. after each treatment.

In the case of a female aged 20 years (Case 3), who was suffering from mitral regurgitation with beginning loss of compensation, observations were made before the baths and immediately after the baths (Table 3). The observations in connection with the ninth, twelfth, fifteenth and sixteenth baths were missed.

Immediately after the first bath there was an increase of 38 mm. in the systolic pressure. The systolic pressure was increased six times,

reduced six times, and was unchanged twice. The increase of systolic pressure amounted to 38 mm., 8 mm., 3 mm., 3 mm., 4 mm. and 6 mm., respectively; an average increase of 10.3 mm. at each bath. The reductions of systolic pressure amounted to 34 mm., 12 mm., 2 mm., 6 mm., 10 mm. and 6 mm., respectively; an average decrease of 11.6 mm. at each bath.

The pulse-pressure was raised seven times, lowered five times, and no change was observed twice. The elevations of pulse-pressure amounted to 16 mm., 11 mm., 5 mm., 3 mm., 3 mm., 3 mm. and 2 mm., respectively, an average elevation of 6.1 mm. at each treatment.

The reductions of the pulse-pressure amounted to 12 mm., 24 mm., 4 mm., 2 mm. and 14 mm., respectively; an average reduction of 11.2 mm. after each treatment.

In the case of a male aged 52 years (Case 9), who was suffering from tachycardia, observations of systolic pressure were made before and after the baths from the sixth to the seventeenth bath inclusive. The results were as follows:

Number of Bath	— Systolic Pressure —	
	Before	After
6	118	140
7	98	110
8	126	130
9	150	124
10	136	136
11	158	130
12	148	150
13	120	150
14	120	132
15	128	130
16	128	136
17	120	140

The systolic pressure was increased nine times, reduced twice, and was unchanged once. The increases of systolic pressure amounted to 22 mm., 12 mm., 4 mm., 2 mm., 30 mm., 12 mm., 2 mm., 8 mm. and 20 mm., respectively; an average of 12.4 mm. at each treatment. The decreases of systolic pressure amounted to 26 mm. and 28 mm., respectively; an average reduction of 27 mm. at each treatment.

In the case of a female aged 57 years (Case 30), who was suffering from fibroid myocarditis, observations of blood-pressure were made before and after each bath for five baths. The blood-pressure observations made the patient excessively nervous and it was necessary to discontinue them after the fifth bath. They were as follows:

No. of Bath	— Before —				— After —			
	Systolic	Diastolic	Mean	Pulse-Pressure	Systolic	Diastolic	Mean	Pulse-Pressure
1	180	130	155	50	210	170	190	40
2	170	150	160	20	184	132	158	52
3	180	118	149	62	214	152	183	62
4	186	132	159	54	164	120	142	44
5	202	150	176	52	176	118	147	58

The systolic pressure was raised three times and lowered twice. The elevations of systolic pressure were 30 mm., 14 mm. and 34 mm., respectively; an average of 26 mm. at each bath. The reductions in systolic pressure were 22 mm. and 26 mm., respectively; an average of 24 mm. and 10 mm., respectively; an average of 10 mm. at each treatment.

The pulse-pressure was increased twice, reduced twice, and was unchanged once. The increases were 32 mm. and 6 mm., respectively; an average of 19 mm. at each treatment. The reductions were 10 mm. and 10 mm. respectively; an average of 10 mm. at each treatment.

TABLE 3.—MITRAL REGURGITATION WITH BEGINNING LOSS OF COMPENSATION.
BLOOD-PRESSURE OBSERVATIONS

No. of Bath	B. P. Before Bath				B. P. After Bath			
	S.	D.	M.	PP.	S.	D.	M.	PP.
1	140	90	115	50	178	140	159	38
2	164	82	123	82	130	72	101	58
3	130	96	113	34	138	88	113	50
4	133	73	103	60	136	65	100.5	71
5	142	83	112.5	59	130	66	98	64
6	136	69	102.5	67	134	71	102.5	63
7	129	69	99	60	132	74	103	58
8	130	66	98	64	134	70	102	64
9*
10	124	69	96.5	55	124	66	95	58
11	128	68	98	60	128	65	96.5	63
12*
13	144	79	111.5	65	138	70	104	68
14	132	58	95	74	138	64	101	74
15*
16*
17	138	80	109	58	128	68	98	60
18	146	76	111	70	140	84	112	56

*Observations missed.

The study of these five cases, two of fibroid myocarditis, one of parenchymatous myocarditis, one of mitral regurgitation with beginning loss of compensation and one of tachycardia, shows that of sixty-six observations made immediately after the administration of the baths the systolic pressure was increased forty-three times, lowered eighteen times, and was unchanged five times. The pulse-pressure was increased twenty-eight times, lowered twenty-one times, and was unchanged five times out of the same number of observations. The highest elevation of systolic pressure recorded was 38 mm. after the first bath in Case 3. The highest elevation of pulse-pressure recorded was 32 mm. after the first bath in Case 30.

Thirty-four observations were made of systolic pressure and pulse-pressure one hour after the baths were given. The systolic pressure was higher than before the bath was given twenty times, lower twelve times, and was unchanged twice. The greatest increase was 19 mm. after the eighteenth bath in Case 1.

The pulse-pressure was raised fourteen times, lowered sixteen times, and was unchanged four times. The highest elevation of pulse-pressure was 28 mm. after the eleventh bath in Case 1.

In these cases we probably get some idea of the effect of the treatment by baths on the blood-pressure. The majority of the observations, however, have had to be made by taking the blood-pressure at the beginning of the treatment and at its close. It must be borne in mind that nearly all of the patients were receiving other forms of treatment as well as carbonated brine baths. In Case 12 the patient received electric light baths alternating with the carbonated brine baths. Cases 8, 13, 38, 66 and 78 received carbonated brine baths on one day and resistance exercises on the alternate day. Case 15 had a carbonated brine bath one day and a Russian bath on the alternate day. Cases 74 and 75 (the same patient) had hot brine baths, massage and various forms of electricity. Cases 63, 64 and 65 (the same patient) had abdominal massage and colonic irrigations in addition to the carbonated brine baths.

All of the patients were in a restful environment, except for inherent restlessness and dissatisfaction on the part of some of them, all were on a carefully regulated diet, the components of which I have already published,^{4, 5} and all were required to rest from one to two hours every day in addition to their time in bed at night, nine hours being prescribed.

ANALYSIS OF CASES

For purposes of analysis the cases may be divided in two ways: those patients who took the full course of treatment of six weeks, sixty; and those who for one reason or another did not complete the full number of baths, twenty-one; second, into the high-pressure cases and the low-pressure cases.

Table 4 gives the reading of the systolic pressure at the beginning and at the end of the treatment in those patients who received the full course of baths. The pressure was higher at the close of the course than at the beginning in thirty instances, lower in twenty-five instances, and was unchanged in five instances. The greatest elevation of pressure was 50 mm. in a case of beginning interstitial nephritis; the greatest reduction 42 mm. in a case of fibroid myocarditis.

Table 5 gives the reading of the systolic pressure in those patients who took only partial courses. At the end of the baths the systolic pressure was found elevated nine times, lowered nine times and unchanged three times. The greatest elevation of pressure was 22 mm. in a case of tachycardia, after twelve baths. The greatest reduction 29 mm. in a case of aortic regurgitation after ten baths.

5. Swan: Interstate Med. Jour., June, 1911, xviii, 633.

Table 6 gives the effect on the diastolic pressure in the cases that received the full course of baths. The diastolic pressure was raised in twenty-six cases, lowered in twenty-eight cases, and no change was noted in six cases. The change in diastolic pressure did not always agree with the change in systolic pressure; when the systolic pressure was elevated the diastolic pressure may have been lowered, and vice versa. The greatest elevation of diastolic pressure was 36 mm. in a case of beginning interstitial nephritis, Case 7. The greatest lowering of diastolic pressure was 27 mm. in a case of fibroid myocarditis, Case 30.

Table 7 gives the details of the diastolic pressure in those patients who had only partial courses. The diastolic pressure was found elevated in eleven cases, lowered in eight cases and unchanged in two cases. The greatest elevation in pressure, 22 mm., was seen in a case of paroxysmal tachycardia, Case 64, after thirteen baths. The greatest lowering of diastolic pressure, 90 mm., was seen in a case of aortic regurgitation, after ten baths.

HIGH-PRESSURE CASES

As the result of the study of 1,000 cases of application for life insurance, Woley⁶ has shown that the average blood-pressure of males at all ages is 127.5 mm., and of females 120 mm. His figures show an increase in the average blood-pressure in each decennial period so that in the sixth decennium the average high pressure is 149 mm., and the average systolic pressure of all applicants in the decennium is 132 mm.

Suppose then, disregarding the ages of the patients, we classify all the cases in this study that give a blood-pressure of over 150 mm. as high-pressure cases. Cases 2, 5, 6, 11, 13, 14, 15, 17, 18, 20, 30, 33, 35, 36, 38, 39, 41, 42, 43, 46, 50, 57, 59, 68, 69, 70, 73, 76 belong to this class.

Table 8 gives the details of the variations of pressure in these cases. It will be seen that the systolic pressure was raised in thirteen cases, lowered in thirteen cases, and was unchanged in two cases. The greatest elevation was 25 mm., in a case of dilatation of the heart (Case 20). The systolic pressure was raised from 186 mm. before the treatments were begun to 212 mm. at their conclusion.

The greatest lowering of systolic pressure was 42 mm., in a case of fibroid myocarditis (Case 35). In this case the systolic pressure was 184 mm. at the beginning of the course of treatment and 142 mm. at its close. The patient had an intermission of seven weeks in his treatment after his fifth bath. At that time his systolic pressure had been reduced from 184 mm. to 168 mm., 16 mm. On resuming his treatment the systolic pressure had further fallen to 150 mm., 18 mm., in spite of the fact that he had been attending to his business. If we exclude this case, the greatest lowering of systolic pressure was 40 mm. in a case of fibroid myocarditis (Case 42).

6. Woley: Jour. Am. Med. Assn., July 9, 1910, iv, 121.

TABLE 4.—SYSTOLIC BLOOD-PRESSURES. COMPLETE COURSES OF CARBONATED BRINE BATHS

No.	Sex	Age	Systolic Pressure at		Difference, mm.	Diagnosis
			Begin. of Treatm't, mm.	End of Treatm't, mm.		
1	M.	76	142	135	— 7	Fibroid Myocarditis.
2	F.	49	153	165	+ 7	Hypertrophy of the heart (Toxic).
3	F.	20	140	145	+ 5	Mitral regurgitation.
4	F.	60	140	152	+12	Fibroid myocarditis.
5	M.	70	168	139	—29	Dilatation of the heart.
6	F.	69	150	162	+12	Fibroid myocarditis.
7	M.	45	124	174	+50	Beginning interstitial nephritis.
8	F.	37	116	124	+ 8	Hypertrophy and dilatation of the heart.
10	F.	56	145	140	— 5	Neurasthenia.
11	M.	36	155	157	+ 2	Hypertrophic cirrhosis of the liver.
12	M.	53	144	128	—16	Dilatation of the heart
13	F.	70	170	170	0	Fibroid myocarditis.
14	F.	77	169	150	—19	Parenchymatous myocarditis.
15	F.	65	178	167	—11	Fibroid myocarditis, chronic bronchitis.
16	F.	26	115	118	+ 3	Parenchymatous myocarditis.
17	M.	67	152	161	+ 9	Chronic parenchymatous nephritis.
18	M.	68	207	190	—17	Mitral regurgitation.
20	M.	63	186	212	+26	Dilatation of heart.
22	M.	36	118	110	— 8	Mitral regurgitation, aortic regurgitation.
23	M.	67	144	140	— 4	Fibroid myocarditis.
24	M.	52	110	104	— 6	Mitral regurgitation.
26	M.	50	150	130	—20	Hypertrophy of the heart.
27	M.	45	109	117	+ 8	Parenchymatous myocarditis.
28	M.	62	135	140	+ 5	Dilatation of the heart.
29	M.	47	124	116	— 8	Dilatation of the heart.
30	F.	57	180	164	—16	Fibroid myocarditis.
32	M.	29	119	134	+15	Parenchymatous myocarditis.
35	M.	71	184	142	—42	Fibroid myocarditis. (Baths in two installments).
40	M.	35	112	102	—10	Parenchymatous myocarditis.
42	F.	54	154	114	—40	Fibroid myocarditis.
43	F.	49	162	142	—20	Hypertrophy and dilatation of the heart.
44	M.	23	120	120	0	Aortic regurgitation.
45	F.	35	120	132	+12	Convalescent from acute infection.
46	F.	60	178	200	+22	Fibroid myocarditis (same as No. 4).
49	F.	48	130	125	— 5	Fat heart.
50	F.	68	193	210	+17	Arteriosclerosis.
51	M.	69	140	135	— 5	Hypertrophy and dilatation of the heart.
52	M.	39	108	110	+ 2	Neurasthenia.
53	M.	54	107	109	+ 2	Hypochondriasis.
54*	F.	26	119	120	+ 1	Convalescent from appendectomy.
55	F.	33	90	95	+ 5	Gastrectasia.
57	F.	47	186	173	—13	Mitral regurgitation.
58	M.	27	126	125	— 1	Nervous dyspepsia.
59	M.	57	199	193	+ 3	Mitral regurgitation.
60	M.	39	119	128	+ 9	Parenchymatous myocarditis, infectious granuloma.
62	M.	60	126	112	—14	Parenchymatous myocarditis.
63	M.	54	150	150	0	Paroxysmal tachycardia.
65	M.	55	113	120	+ 7	Paroxysmal tachycardia (Same patient as No. 63).
66	M.	60	148	138	—10	Fibroid myocarditis.
67	M.	61	144	144	0	Mitral regurgitation (Same patient as No. 66).

*When the last observation was made on this patient she had just developed acute bronchitis.

TABLE 4.—SYSTOLIC BLOOD-PRESSURES. COMPLETE COURSES OF CARBONATED BRINE BATHS
(Continued)

No.	Sex	Age	Systolic Pressure at		Difference, mm.	Diagnosis
			Begin. of Treatm't, mm.	End of Treatm't, mm.		
68 F.	51	198	199	+ 1	Hypertrophy and dilatation of the heart.
69 F.	52	170	170	0	Hypertrophy and dilatation of the heart. (Same patient as No. 68.)
73 F.	60	170	184	+14	Fibroid myocarditis.
74 M.	56	112	120	+ 8	Arthritis deformans with myocardial insufficiency.
75 M.	56	118	125	+ 7	Same patient as No. 74.
76 M.	71	162	168	+ 6	Dilatation of the heart. (Same patient as No. 5.)
77 F.	70	140	138	— 2	Fibroid myocarditis.
78 M.	36	116	115	— 1	Dilatation of the heart. (Same patient as No. 25.)
80 F.	54	118	122	+ 4	Dilatation of the heart. (Same patient as No. 37.)
81 F.	49	130	156	+26	Hypertrophy of the heart. (Same patient as No. 2 after operation.)

TABLE 5.—SYSTOLIC BLOOD-PRESSURE. INCOMPLETE CARBONATED BRINE COURSES

No.	Sex	Age	Systolic Pressure at		Differ- ence, mm.	No. of Baths	Diagnosis
			Begin. of Treatm't, mm.	End of Treatm't, mm.			
9 M.	52	118	140	+22	12	Tachycardia
19 M.	57	134	134	0	6	Dilatation of heart.
21 M.	53	100	100	0	11	Fibroid myocarditis. Subacute bronchitis.
25 M.	35	130	116	—14	9	Dilatation of heart.
31 F.	65	125	119	— 6	9	Weak heart muscle.
33 M.	52	188	168	—20	3	Aortic regurgitation.
34 M.	58	120	120	0	11	Fibroid myocarditis.
36 M.	72	188	199	+11	9	Fibroid myocarditis.
37 F.	53	124	115	— 9	11	Beginning arteriosclerosis.
38 F.	70	162	140	—22	11	Diabetes mellitus.
39 F.	45	185	180	— 5	9	Convalescent from operation.
41 M.	58	156	166	+10	11	Hypertrophy of the heart.
47 F.	19	109	118	+ 9	11	Convalescent from typhoid fever.
48 M.	62	105	120	+15	11	Parenchymatous myocarditis.
56 M.	38	108	120	+12	9	Parenchymatous myocarditis.
61 M.	77	149	135	—14	12	Hypertrophy of the heart.
64 M.	54	125	136	+11	13	Paroxysmal tachycardia (same patient as No. 63).
70 M.	30	174	145	—29	10	Aortic regurgitation.
71 M.	35	115	125	+10	8	Pulmonary emphysema.
72 M.	48	110	115	+ 5	7	Convalescent from influenza.
79 M.	52	137	130	— 7	5	Dilatation of the heart.

TABLE 6.—DIASTOLIC BLOOD-PRESSURE, COMPLETE CARBONATED BRINE COURSES

No.	Sex	Age	Diastolic Pressure at		Difference, mm.
			Begin. of Treatment, mm.	End of Treatment, mm.	
1	M	76	85	80	— 5
2	F	49	108	104	— 4
3	F	20	90	80	—10
4	F	60	86	70	—16
5	M	70	96	80	—16
6	F	69	84	79	— 5
7	M	45	90	126	+36
8	F	37	74	74	0
10	F	56	70	75	+ 5
11	M	36	92	90	— 2
12	M	53	80	75	— 5
13	F	70	112	105	— 7
14	F	77	94	76	—18
15	F	65	92	100	+ 8
16	F	26	60	62	+ 3
17	M	67	93	80	—13
18	M	68	110	100	—10
20	M	63	100	108	+ 8
22	M	36	75	95	+20
23	M	67	80	85	+ 5
24	M	52	72	68	— 4
26	M	50	90	83	— 7
27	M	45	66	69	+ 3
28	M	62	92	103	+11
29	M	47	83	72	—11
30	F	57	130	103	—27
32	F	29	75	82	+ 7
35	M	71	118	88	—30
40	M	35	70	70	0
42	F	54	112	76	—46
43	F	49	112	86	—36
44	M	23	50	36	—14
45	F	35	82	72	—10
46	F	60	90	80	—10
49	F	48	78	90	+12
50	F	68	85	79	— 6
51	M	69	75	75	0
52	M	39	62	76	+14
53	M	54	60	78	+18
54	F	26	67	80	+13*
55	F	33	55	75	+20
57	F	47	103	105	+ 2
58	M	27	70	80	+10
59	M	57	119	125	+ 6
60	M	39	78	78	0
62	M	60	98	75	—23
63	M	54	93	90	— 3
65	M	55	70	70	0
66	M	60	76	76	0
67	M	61	62	68	+ 6
68	F	51	100	90	—10
69	F	52	85	95	+10
73	F	60	85	87	+ 2
74	M	56	75	78	+ 3
75	M	56	102	80	—22
76	M	71	84	90	+ 6
77	F	70	70	72	+ 2
78	M	36	73	75	+ 2
80	F	54	70	68	— 2
81	F	49	95	125	+30

*When the last observation was made on this patient she had just developed acute bronchitis.

TABLE 7.—DIASTOLIC BLOOD-PRESSURES, INCOMPLETE CARBONATED BRINE COURSES

No.	Sex	Age	Diastolic Pressure at		Difference, mm.	No. of Baths
			Begin. of Treatment, mm.	End of Treatment, mm.		
9	M	52	80	100	+20	12
19	M	57	96	100	+ 4	6
21	M	53	62	64	+ 2	11
25	M	35	78	80	+ 2	9
31	F	65	81	70	—11	9
33	M	52	78	70	— 8	3
34	M	58	84	84	0	11
36	M	72	100	96	— 4	9
37	F	53	70	71	+ 1	11
38	F	70	76	72	— 4	11
39	F	45	95	95	0	9
41	M	58	104	110	+ 6	11
47	F	19	58	64	+ 6	11
48	M	62	65	66	+ 1	11
56	M	38	65	74	+ 9	9
61	M	77	88	83	— 5	12
64	M	54	82	104	+22	13
70	M	30	90	0	—90	10
71	M	35	80	78	— 2	8
72	M	48	72	65	— 7	7
79	M	52	85	86	+ 1	5

TABLE 8.—HIGH PRESSURE CASES, SYSTOLIC PRESSURE ABOVE 150 MM.

Case No.	Variation of Pressure			Pulse	Number of Baths
	Systolic	Diastolic	Mean		
2	+ 7	— 4	+ 1.5	+11	18
5	—29	—16	—22.5	—13	18
6	+12	— 5	+ 3.5	+16	18
11	+ 2	— 2	0	+ 4	18
13	0	— 7	— 3.5	+ 7	18
14	—19	—18	—18.5	— 1	18
15	—11	+ 8	— 1.5	—19	18
17	+ 9	—13	— 2	+22	18
18	—17	—10	—13.5	— 7	18
20	+26	+ 8	+17	+18	18
30	—16	—27	—21.5	+11	18
33	—26	— 8	—14	—12	3
35	—42	—30	—36	—12	18
36	+11	— 4	+ 3.5	+15	9
38	—22	— 4	—13	—18	11
39	— 5	0	— 2.5	— 5	9
41	+10	+ 6	+ 8	+ 4	11
42	—40	—46	—43	+ 6	18
43	—20	—36	—23	+ 6	18
46	+22	—10	+ 6	+32	18
50	+17	— 6	+ 5.5	+23	18
57	—13	+ 2	— 5.5	—15	18
59	+ 3	+ 6	+ 4.5	— 3	18
68	+ 1	—10	— 4.5	+11	18
69	0	+10	+ 5	—10	18
70	—29	—90	—59.5	+61	10
73	+14	+ 2	+ 8	+12	18
76	+ 6	+ 6	+ 6	0	18

TABLE 9.—LOW PRESSURE CASES. SYSTOLIC PRESSURE 150 MM., OR BELOW

Case No.	Variation of Pressure			Pulse	Number of Baths
	Systolic	Diastolic	Mean		
1	— 7	— 5	— 6	— 2	18
3	+ 5	—10	— 3.5	+15	18
4	+12	—16	— 2	+28	18
7	+50	+36	+43	+14	18
8	+ 8	0	+ 4	+ 8	18
9	+22	+20	+21	+ 2	12
10	— 5	+ 5	0	—10	18
12	—16	— 5	—10.5	— 9	18
16	+ 3	+ 3	+ 3	0	18
19	0	+ 4	+ 2	— 4	6
21	0	+ 2	+ 1	— 2	11
22	— 8	+20	+ 6	—28	18
23	— 4	+ 5	+ 0.5	— 9	18
24	— 6	— 4	— 5	— 2	18
25	—14	+ 2	— 6	—16	9
26	—20	— 7	—13.5	—13	18
27	+ 8	+ 3	+ 5.5	— 5	18
28	+ 5	+11	+ 8	— 6	18
29	— 8	—11	— 9.5	— 3	18
31	— 6	—11	— 8.5	+ 5	9
32	+15	+ 7	+11	+ 8	18
34	0	0	0	0	17
37	— 9	+ 1	— 4	—10	11
40	—10	0	— 5	—10	18
44	0	—14	— 7	+14	18
45	+12	—10	+ 1	+12	18
47	+ 9	+ 6	+ 7.5	+ 3	11
48	+15	+ 1	+ 8	+14	11
49	— 5	+12	+ 3.5	—17	18
51	— 5	0	— 2.5	— 5	18
52	+ 2	+14	+ 8	—12	18
53	+ 2	+18	+10	—16	18
54	+ 1	+13	+ 7	—12	18
55	+ 5	+20	+12.5	—15	18
56	+12	+ 9	+10.5	+ 3	9
58	— 1	+10	+ 4.5	—11	18
60	+ 9	0	+ 4.5	+ 9	18
61	—14	— 5	— 9.5	— 9	12
62	—14	—23	—18.5	+ 9	18
63	0	— 3	— 1.5	+ 2	18
64	+11	+22	+16.5	—11	13
65	+ 7	0	+ 3.5	+ 7	18
66	—10	0	— 5	—10	18
67	0	+ 6	+ 3	— 6	18
71	+10	— 2	+ 4	+22	8
72	+ 5	— 7	— 1	+12	7
74	+ 8	+ 3	+ 5.5	+ 5	18
75	+ 7	—22	— 7.5	+29	18
77	— 2	+ 2	0	— 4	18
78	— 1	+ 2	+ 9.5	— 3	18
79	— 7	+ 1	— 3	— 8	5
80	+ 4	— 2	+ 1	+ 6	18
81	+26	+30	+28	— 4	18

The diastolic pressure was raised in eight cases, lowered in nineteen cases, and was unchanged in one case. The greatest elevation was 8 mm. in two cases; one of fibroid myocarditis with chronic bronchitis (Case 15), and one of dilatation of the heart (Case 20). In the former the diastolic pressure was 92 mm. at the beginning of the treatments and 100 mm. at the end; in the latter the diastolic pressure rose from 100 mm., at the beginning of the treatments, to 108 mm. at their close.

The greatest reduction of diastolic pressure was 90 mm., in a case of aortic regurgitation (Case 70) after ten treatments. In a case of hypertrophy and dilatation of the heart (Case 43) the diastolic pressure was reduced 36 mm.; from 112 mm. at the beginning of the treatments to 86 mm. at their close. In a case of myocarditis (Case 42) the diastolic pressure was reduced 46 mm.; from 112 mm. at the beginning of the baths to 76 mm. at the end.

The mean pressure in these cases was raised eleven times, lowered sixteen times and was unchanged once. The greatest elevation of the mean pressure was 17 mm., in a case of dilatation of the heart (Case 20). The greatest reduction of mean pressure was 59.5 mm., in a case of aortic regurgitation (Case 70).

The pulse-pressure in these cases was raised sixteen times, reduced eleven times and was unchanged once. The greatest elevation of pulse-pressure was 61 mm., in a case of aortic regurgitation (Case 70). The greatest reduction in pulse-pressure was 19 mm., in a case of fibroid myocarditis with chronic bronchitis (Case 15).

Case 70 was a case of aortic regurgitation in a young man, aged 30 years. On admission he had dilatation of the heart as well as hypertrophy, and the murmur of mitral regurgitation, as well as a double aortic murmur. The aortic diastolic murmur, however, was not loud and was not well transmitted. His blood-pressure showed a well-marked fifth phase at 90 mm., giving him a pulse-pressure of 84 mm.

After ten carbonated brine baths, which were given in groups of three baths with an interval of one day between each group of baths, the transverse diameter of his cardiac dulness was found to be $3\frac{3}{4}$ inches instead of $5\frac{3}{4}$ inches, which was the record on admission. The point of maximum intensity of the cardiac impulse had moved in from $5\frac{3}{4}$ inches to the left of the midsternal line in the sixth interspace, to the midclavicular line in the sixth interspace. The murmur of mitral regurgitation, although still present, was not as loud as it had been and was not transmitted to the angle of the scapula. The murmur of aortic regurgitation was still present. The pulse was more positively of the Corrigan type. The blood-pressure observations gave a systolic reading of 145 mm.; but there were no phases. The tap could be heard with no pressure in the cuff. Consequently, the diastolic pressure could be considered 0, the mean pressure 72.5 and the pulse-pressure 145.

Gitting,⁷ and Goodman and Howell^{8,9} have pointed out the absence of phases and a diastolic pressure of 0 in cases of aortic regurgitation.

LOW-PRESSURE CASES

Cases 1, 3, 4, 7, 8, 9, 10, 12, 16, 19, 21, 22, 23, 24, 25, 26, 27, 28, 29, 31, 32, 34, 37, 40, 44, 45, 47, 48, 49, 51, 52, 53, 54, 55, 56, 58, 60, 61, 62, 63, 64, 65, 66, 67, 71, 72, 74, 75, 77, 78, 79, 80 and 81 may be looked on as low-pressure cases (Table 9). In these the systolic pressure was raised in twenty-six cases, reduced in twenty-one cases and was unchanged in six cases. The greatest increase in systolic pressure was 50 mm., in a case of beginning interstitial nephritis (Case 7). The patient had a systolic pressure of 124 mm. at the beginning of the treatments, and at the end of the course his systolic pressure had increased to 174 mm.

The greatest reduction of systolic pressure was 20 mm., in a case of hypertrophy of the heart (Case 26). The systolic pressure was 150 mm. at the beginning of the treatments, and 130 mm. at the end.

The diastolic pressure was increased in twenty-nine cases, reduced in seventeen cases and was unchanged in seven cases. The greatest elevation of diastolic pressure was 36 mm., in a case of beginning interstitial nephritis (Case 7). The patient had a diastolic pressure of 90 mm. at the beginning of the treatments, and 126 mm. at their close. The greatest reduction of diastolic pressure was 23 mm., in a case of parenchymatous myocarditis (Case 62). At the beginning of the treatments the diastolic pressure was 98 mm., and at their close it was 75 mm. This patient was 60 years of age.

The mean pressure was elevated in thirty cases, reduced in twenty cases and was unchanged in three cases. The greatest increase in mean pressure was 43 mm., in a case of beginning interstitial nephritis (Case 7). The greatest decrease in mean pressure was 18.5 mm., in a case of parenchymatous myocarditis (Case 62).

The pulse-pressure was elevated in twenty-three cases, reduced in thirty cases and was unchanged in two cases. The greatest elevation of pulse-pressure was 29 mm., in a case of arthritis deformans with myocardial insufficiency (Case 75). The greatest reduction in pulse-pressure was 28 mm. in a case of mitral regurgitation and aortic regurgitation (Case 22).

FIBROID MYOCARDITIS

Cases 1, 4, 6, 13, 15, 21, 23, 30, 34, 35, 36, 42, 46, 66, 73 and 77 are cases of fibroid myocarditis (Table 10).

7. Gittings: *THE ARCHIVES INT. MED.*, August, 1910, vi, 196.

8. Goodman and Howell: *Univ. Penn. Med. Bull.*, November, 1910, xxiii, 469.

9. Goodman and Howell: *Am. Jour. Med. Sc.*, September, 1911, cxliii, 334.

In these cases the systolic pressure was raised in five, reduced in eight and no change was noted in three. The greatest elevation of systolic pressure was 22 mm., in Case 46; the greatest reduction was 42 mm., in Case 35.

The diastolic pressure was raised in five cases, reduced in nine cases and was unchanged in two cases. The greatest elevation was 8 mm., in Case 15; the greatest reduction 30 mm., in Case 35.

The mean pressure was raised in six cases, lowered in eight cases, and was unchanged in two cases. The greatest elevation of mean pressure was 8 mm., in Case 73; the greatest reduction was 43 mm., in Case 42.

The pulse-pressure was increased in eight cases, reduced in seven cases and was unchanged in one case. The greatest elevation of pulse-pressure was 32 mm., in Case 46; the greatest reduction was 19 mm., in Case 15.

TABLE 10.—CASES OF FIBROID MYOCARDITIS

Case No.	Variation of Pressure				Number of Baths
	Systolic	Diastolic	Mean	Pulse	
1	— 7	— 5	— 6	— 2	18
4	+12	—16	— 2	+28	18
6	+12	— 5	+ 3.5	+16	18
13	0	— 7	— 3.5	+ 7	18
15	—11	+ 8	— 1.5	—19	18
21	0	+ 2	+ 1	— 2	11
23	— 4	+ 5	+ 0.5	— 9	18
30	—16	—27	—21.5	+11	18
34	0	0	0	0	11
35	—42	—30	—36	—12	18
36	+11	— 4	+ 3.5	+15	9
42	—40	—46	—43	+ 6	18
46	+22	—10	+ 6	+32	18
66	—10	0	— 5	—10	18
73	+14	+ 2	+ 8	+12	18
77	— 2	+ 2	0	— 4	18

PARENCHYMATOUS MYOCARDITIS

Cases 14, 16, 27, 32, 40, 48, 56, 60 and 62 are cases of parenchymatous myocarditis (Table 11).

The systolic pressure was raised in six of these cases and was reduced in three. The greatest elevation of systolic pressure was 15 mm., in Cases 32 and 48; the greatest reduction was 19 mm., in Case 14.

The diastolic pressure was raised in five cases, lowered in two cases, and was unchanged in two cases. The greatest elevation was 9 mm., in Case 56; the greatest reduction was 23 mm., in Case 62.

The mean pressure was raised in six cases and lowered in three cases. The greatest elevation was 11 mm., in Case 32; the greatest reduction was 18.5 mm., in Cases 14 and 62.

The pulse-pressure was increased in five cases, reduced in three cases and was unchanged in one case. The greatest elevation of pulse-pressure was 14 mm., in Case 48; the greatest reduction was 10 mm., in Case 40.

TABLE 11.—CASES OF PARENCHYMATOUS MYOCARDITIS

Case No.	Variation of Pressure				Number of Baths
	Systolic	Diastolic	Mean	Pulse	
14	-19	-18	-18.5	- 1	18
16	+ 3	+ 3	+ 3	0	18
27	+ 8	+ 3	+ 3.5	- 5	18
32	+15	+ 7	+11	+ 8	18
40	-10	0	- 5	-10	18
60	+ 9	0	+ 4.5	+ 9	18
62	-14	-23	-18.5	+ 9	18
48	+15	+ 1	+ 8	+14	11
56	+12	+ 9	+10.5	+ 3	9

DILATATION OF THE HEART

Cases 5, 12, 19, 20, 25, 28, 29, 76, 78, 79 and 80 are cases of dilatation of the heart (Table 12).

In four of these cases the systolic pressure was raised; in six it was lowered and in one no change was noted. The greatest elevation of systolic pressure was 26 mm., in Case 20; the greatest depression was 29 mm., in Case 5.

The diastolic pressure was raised in seven cases and lowered in four. The greatest elevation of diastolic pressure was 11 mm., in Case 28; the greatest reduction was 16 mm., in Case 5.

The mean pressure was raised in six cases and lowered in five cases. The greatest elevation was 17 mm., in Case 20; the greatest reduction was 22.5 mm., in Case 5.

The pulse-pressure was raised in two cases, lowered in eight cases and no change was noted in one case. The greatest increase in pulse-pressure was 18 mm., in Case 20; the greatest decrease was 16 mm., in Case 25.

TABLE 12.—CASES OF DILATATION OF THE HEART

Case No.	Variation of Pressure				Number of Baths
	Systolic	Diastolic	Mean	Pulse	
5	-29	-16	-22.5	-13	18
12	-16	- 5	-10.5	- 9	18
19	0	+ 4	+ 2	- 4	6
20	+26	+ 8	+17	+18	18
25	-14	+ 2	- 6	-16	9
28	+ 5	+11	+ 8	- 6	18
29	- 8	-11	- 9.5	- 3	18
76	+ 6	+ 6	+ 6	0	18
78	- 1	+ 2	+ 0.5	- 3	18
79	- 7	+ 1	- 3	- 8	5
80	+ 4	- 2	+ 1	+ 6	18

HYPERTROPHY AND DILATATION OF THE HEART

Cases 8, 43, 51, 68 and 69 are cases of hypertrophy and dilatation of the heart (Table 13).

The systolic pressure in these cases was raised twice, lowered twice and no change was observed once. The greatest increase in systolic pressure was 8 mm., in Case 8; the greatest decrease of systolic pressure was 20 mm., in Case 43.

The diastolic pressure was raised once, lowered twice and no change was noted twice. The elevation amounted to 10 mm., in Case 69. The greatest reduction of diastolic pressure was 36 mm., in Case 43.

The mean pressure was raised twice and lowered three times. The greatest elevation of mean pressure was 5 mm., in Case 69; the greatest reduction was 23 mm., in Case 43.

The pulse-pressure was raised three times and lowered twice. The greatest elevation of pulse pressure was 11 mm., in Case 68; the greatest decrease in pulse-pressure was 10 mm., in Case 69.

TABLE 13.—CASES OF HYPERTROPHY AND DILATATION OF THE HEART

Case No.	Variation of Pressure				Number of Baths
	Systolic	Diastolic	Mean	Pulse	
8	+ 8	0	+ 4	+ 8	18
43	-20	-36	-23	+ 6	18
51	- 5	0	- 2.5	- 5	18
68	+ 1	-10	- 4.5	+11	18
69	0	+10	+ 5	-10	18

MITRAL REGURGITATION

Cases 18, 24, 57, 59 and 67 are cases of mitral regurgitation (Table 14). In these cases the systolic pressure was raised once, reduced three times and no change was observed once. The increase of systolic pressure amounted to 3 mm., in Case 59. The greatest reduction of systolic pressure amounted to 17 mm., in case 63.

The diastolic pressure was raised in three cases and was reduced in two cases. The greatest increase of diastolic pressure was 6 mm., in Cases 59 and 67. The greatest reduction of diastolic pressure was 10 mm., in Case 18.

The mean pressure was raised twice and lowered three times. The greatest increase of mean pressure was 4.5 mm., in Case 59. The greatest decrease of mean pressure was 13.5 mm., in Case 18.

The pulse-pressure was reduced in every case; the greatest reduction was 15 mm., in Case 57.

TABLE 14.—CASES OF MITRAL REGURGITATION

Case No.	Variation of Pressure				Number of Baths
	Systolic	Diastolic	Mean	Pulse	
18	-17	-10	-13.5	- 7	18
24	- 6	- 4	- 5	- 2	18
57	-13	+ 2	- 5.5	-15	18
59	+ 3	+ 6	+ 4.5	- 3	18
67	0	+ 6	+ 3	- 6	18

HYPERTROPHY OF THE HEART

Cases 2, 26, 41, 61 and 81 are cases of hypertrophy of the heart (Table 15). In these cases the systolic pressure was increased in three and reduced in two. The greatest increase of systolic pressure was 26 mm., in Case 81. The greatest reduction in systolic pressure was 20 mm., in Case 26.

The diastolic pressure was increased in two cases and reduced in three cases. The greatest increase of diastolic pressure was 30 mm., in Case 81; the greatest reduction of diastolic pressure was 7 mm., in Case 26.

The mean pressure was increased in three cases and reduced in two. The greatest increase in mean pressure was 28 mm., in Case 81 and the greatest reduction in mean pressure was 13.5 mm., in Case 26.

The pulse-pressure was increased in two cases and reduced in three cases. The greatest increase in pulse-pressure was 11 mm., in Case 2; the greatest reduction in pulse-pressure was 13 mm., in Case 26.

TABLE 15.—CASES OF HYPERTROPHY OF THE HEART

Case No.	Variation of Pressure				Number of Baths
	Systolic	Diastolic	Mean	Pulse	
2	+ 7	— 4	+ 1.5	+11	18
26	—20	— 7	—13.5	—13	18
41	+10	+ 6	+ 8	+ 4	11
61	—14	— 5	— 9.5	— 9	12
81	+26	+30	+28	— 4	18

TACHYCARDIA

Cases 9, 63, 64 and 65 are cases of tachycardia (Table 16). The systolic pressure was increased in three of these cases and no change was noted in the other one. The greatest increase of systolic pressure was 22 mm., in Case 9.

The diastolic pressure was increased in two of the cases; diminished in one, and no change was noted in the other one. The greatest increase of diastolic pressure was 22 mm., in Case 64. The reduction of diastolic pressure was 3 mm., in Case 63.

The mean pressure was raised in three of the cases and lowered in one. The greatest elevation of mean pressure was 21 mm., in Case 9. The reduction of mean pressure was 1.5 mm., in Case 63.

The pulse-pressure was increased in three of the cases and reduced in the other one. The greatest increase of pulse-pressure was 7 mm., in Case 65; the reduction of pulse pressure was 11 mm., in Case 64.

TABLE 16.—CASES OF TACHYCARDIA

Case No.	Variation of Pressure				Number of Baths
	Systolic	Diastolic	Mean	Pulse	
9	+22	+20	+21	+ 2	12
63	0	— 3	— 1.5	+ 3	18
64	+11	+22	+16.5	—11	13
65	+ 7	0	+ 3.5	+ 7	18

AORTIC REGURGITATION

Cases 33, 44 and 70 are cases of aortic regurgitation (Table 17). The systolic pressure was diminished in two of these cases and no change was noted in the other one. The greatest reduction of pressure was 29 mm., in Case 70.

The diastolic pressure was reduced in all three cases. The greatest reduction was 90 mm., in Case 70.

The mean pressure was reduced in all three of the cases. The greatest reduction was 59.5 mm., in Case 70.

The pulse pressure was increased in two of the cases and diminished in the third. The greatest increase of pulse-pressure was 61 mm., in Case 70; the diminution of pulse-pressure amounted to 12 mm., in Case 33.

TABLE 17.—CASES OF AORTIC REGURGITATION

Case No.	Variation of Pressure				Number of Baths
	Systolic	Diastolic	Mean	Pulse	
33	-20	- 8	-14	-12	3
44	0	-14	- 7	+14	18
70	-29	-90	-59.5	+61	10

ARTERIOSCLEROSIS

Cases 37 and 50 are cases of arteriosclerosis (Table 18). In one of these cases the systolic pressure was increased and in the other one it was diminished. The diastolic pressure, the mean pressure and the pulse-pressure were increased in one case and diminished in the other.

TABLE 18.—CASES OF ARTERIOSCLEROSIS

Case No.	Variation of Pressure				Number of Baths
	Systolic	Diastolic	Mean	Pulse	
37	- 9	+ 1	- 4	-10	11
50	+17	- 6	+ 5.5	+23	18

In the case of mitral obstruction and regurgitation (Case 3), the systolic pressure was increased, the diastolic pressure and the mean pressure were reduced, and the pulse-pressure was increased.

In the case of chronic parenchymatous nephritis (Case 17), the systolic pressure was increased; the diastolic and mean pressure were reduced, and the pulse-pressure was increased.

In the case of beginning interstitial nephritis (Case 7), the systolic pressure was increased 50 mm.; the diastolic pressure was increased 36 mm.; the mean pressure was increased 43 mm., and the pulse-pressure was increased 14 mm.

In the case of mitral regurgitation and aortic regurgitation (Case 22), the systolic pressure was reduced; the diastolic and mean pressure were increased and the pulse-pressure was reduced.

In the case of fat heart (Case 49), the systolic pressure was reduced, the diastolic pressure and the mean pressure were increased and the pulse-pressure was reduced.

In the case of weak heart (Case 30), the systolic pressure, the diastolic pressure and the mean pressure were reduced, but the pulse-pressure was increased.

CONCLUSIONS

1. Carbonated brine baths have no constant effect on the blood-pressure of the human subject.

2. In the cases in which observations were made both before and after each bath the systolic pressure was raised more frequently than it

was lowered; so that we may say that the tendency of the baths is to raise the blood-pressure.

3. Although there are cases of high blood-pressure in which a course of carbonated brine baths has been followed by a lower systolic pressure, there are other cases of high-pressure in which the pressure has been higher at the end of the course of treatment than it was at the beginning; in one case 26 mm. higher.

4. Although there are cases of low blood-pressure in which a course of carbonated brine baths has been followed by a higher systolic pressure, there are other cases of low pressure in which the pressure has been lower at the end of the course of treatment than it was at the beginning; in one case 20 mm. lower.

5. There is no method of determining in advance whether a given treatment will be followed by an elevation or by a fall of pressure.

6. In the eighty-one cases the systolic pressure was higher at the end of the course of treatment than at the beginning in thirty-nine; lower in thirty-four, and unchanged in eight.

7. In cases of fibroid myocarditis the pressure effect is inconstant. In this series of cases the systolic pressure was lowered more often than it was raised; but the pulse-pressure was raised more often than it was lowered. It seems to me a dangerous procedure to use a form of treatment in a case of cardiac fibrosis which may be followed by an increase of systolic pressure of 22 mm., or an increase of pulse-pressure of 32 mm.

8. In cases of parenchymatous myocarditis the effect of the baths on blood-pressure is usually to raise it; but in some cases the baths are followed by a reduction of both the systolic and the pulse-pressures.

9. In cases of dilatation of the heart, cases of hypertrophy and dilatation of the heart, cases of mitral regurgitation, cases of hypertrophy of the heart, cases of tachycardia, and cases of aortic regurgitation, the same uncertainty of results was seen, except that in cases of mitral regurgitation the pulse-pressure was reduced in every one of the five cases; and in cases of aortic regurgitation the diastolic pressure and the mean pressure were reduced in every one of three cases.

10. In a case of arteriosclerosis an increase of 17 mm. in the systolic pressure and 23 mm. in pulse-pressure might result disastrously. In a case of chronic parenchymatous nephritis an increase of 9 mm. in systolic pressure and of 22 mm. in pulse-pressure may or may not be negligible. In a case of interstitial nephritis an increase of 50 mm. in systolic pressure could hardly be thought desirable.

11. The reduction of systolic pressure in a case of weak heart can scarcely be looked on as a favorable circumstance.

12. The benefit in the subjective symptoms in cases of heart disease which follows a course of carbonated brine baths is not dependent on the influence of the treatment on the blood-pressure.

A CLINICAL STUDY OF THE EFFECTS OF SLEEP AND REST ON BLOOD-PRESSURE *

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AND

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Numerous physiological researches on both man and the lower animals have shown that there is a marked fall in blood-pressure during sleep. Tarchanoff¹ showed that a fall in aortic pressure of from 20 to 50 mm. mercury took place in young dogs during the early stages of sleep, and Howell² noted a like fall in the blood-pressure of man.

Leonard Hill,³ although admitting that a fall in pressure took place, did not believe that this drop was any greater during sleep than that which has been demonstrated to occur as a result of simple rest combined with the prone posture. Brush and Fayerweather,⁴ however, showed definitely that this was not the case, but that the fall was concurrent with sleep, and that it was much greater than the drop which sometimes, but not invariably, takes place simply from rest or on lying down.

Howell (Textbook) brings out the important fact that the maximum fall occurs between one and two hours after sleep, and that this same period corresponds to the time of the greatest auditory insensibility, as determined by Kohlschutter, Czerny, and by Morgenthal and Presbergen.

Our attention was first called to these physiological facts in the course of the study of a case of a peculiar mental and spinal phenomena, manifested in an instance of disturbed cerebrospinal circulation. Further investigation conducted on carefully selected cases showed that in each individual a more or less constant variation in the blood-pressure occurred, depending apparently more on the time of observation than on other factors. For example, we found that the night pressures, taken in groups of night sleepers, were almost invariably lower than the day pressures in the same individuals, but that conversely in night workers (ten instances studied) and day sleepers the finding was reversed. In the

* Read at the meeting of the Association of American Physicians, May 14, 1912.

* From the Second Medical Service, City Hospital.

* Manuscript submitted for publication, May 22, 1912.

1. Tarchanoff: *Arch. Ital. de Biol.*, 1894. xxi, 318.

2. Howell: *Jour. Exp. Med.*, 1897. ii, 335.

3. Hill: *Lancet*, London. 1898. i, 282.

4. Brush and Fayerweather: *Am. Jour. Physiol.*, 1901. v. 199.

hope that a careful study of these conditions might lead to an understanding of the subject which might be utilized clinically, we then undertook a quite extensive study of the subject, after we had first verified on patients the correctness as applied to them, of the general physiological facts above cited.

All of our observations were made using the 12 cm. stiff leather arm cuff, and in most instances either the Janeway or the Sahli sphygmomanometers were employed. For obvious reasons the study was confined to the systolic pressure. In most instances observations on individuals or groups of cases were corrected or verified by subsequent repetition under as nearly as possible the same conditions. In so far as practical, neurotic individuals and such others as through personal peculiarities, would be likely to confuse or complicate the main points of our study were avoided or eventually excluded from the statistical study, and an effort was made to select such instances as would appear to apply most fittingly to the question immediately under discussion, although these aberrant cases afforded a rich material of great interest. Naturally it was found that phlegmatic subjects showed much less hourly variations, such as might be excited by psychic stimulation; for this reason neurotic subjects were avoided in so far as possible, or their records were discarded when the data were considered statistically.

For convenience of study and purely from the clinical standpoint, we have divided our series of carefully observed cases into three classes. Those in which the systolic pressure lay within the range of the usual, 110 to below 170 mm. Hg; those in which the pressure was less than the usual, that is below 110 mm., and those in which the pressure was above 170 mm. Hg, which class comprised the high-pressure cases. In order that widely discordant results might not be reached from this division into more or less arbitrary classes, excessive alterations in pressure were not included in our tabulated series, though special but entirely individual studies have been made in many such instances. Thus, for example, the very low systolic pressure of 65 mm. in a case of salvarsan poisoning was not included, nor were two instances of systolic pressure of 300 and 310 mm., respectively, included.

In each series a basis of comparison was established by taking the pressure in each case between 4 and 5 p. m., for, as we have shown, the time of the day, at least in its relation to rhythmic sleep, is an important matter when one comes to comparatively estimate and particularly to value blood-pressure. Each group was investigated and recorded not less than four times, and most cases were kept on regular pressure charts throughout.

Sixty-eight patients who showed medium pressures were studied. These gave an average basic afternoon pressure of 142.5 mm. Systolic

readings taken between one and two hours after the night sleep showed an average drop of 24 mm. Hg. Three hours after the morning waking the pressure still showed an average depression of 12 mm., and from this time during the day the pressure gradually rose until the mean afternoon level was again reached, between 4 and 5 o'clock.

Thirty instances of low pressure were similarly studied. The group showed an average systolic pressure of 100 mm. (the minimum case had a pressure of 80 mm.). Pressure determined within from one to two hours after primary sleep showed an average drop of 16.5 mm. The morning reading still showed an average depression of 6.66 mm. with a slow return to the general average of evening pressure.

Twenty-nine cases of high-pressure with an average systolic reading of 204.5 and a maximum in two cases of 250 mm., showed an average one- to two-hour drop of 44.8 mm. and a morning pressure of 22.8.

It is a noteworthy fact that the least drop in pressure took place in those patients who had an initial low-pressure and the greatest fall in those with the highest systolic reading. Study of isolated examples of very high and of very low pressure show this fact in even more marked degree. Just as under physiological conditions the maximum fall occurs within two hours after falling asleep, with a subsequent slow rise culminating in the afternoon reading.

That this fall is a definite attempt at conservation on the part of nature, needs no very vivid imagination to conceive.

Observations conducted on these and other groups of selected cases, including also neurotic subjects, indicate that the preliminary drop after sleep is a very rapid one and that the rise thereafter begins during sleep, very soon after the point of minimum pressure and extends up gradually through the remainder of the sleep period, to slowly rise during the day until the maximum pressure of the afternoon is reached. This is the course when patients are confined to bed, but when they are allowed to rise and go about the ward there is a slight but rapid rise of a few mm. incident to getting up, after which the usual slow upward curve ensues, and except in this particular no essential difference between bed and ambulatory cases is demonstrable.

Although it might reasonably be inferred from the foregoing that a regular blood-pressure curve exists not only in normal but also in super- and subnormal cases, and while such is true of the average case, many exceptions exist, especially in subjects markedly influenced by various psychic factors and particularly as we have demonstrated to our own satisfaction in cases of circulatory decompensation or in cases about to decompensate.

The marked effect of nervousness and apprehension in influencing the blood-pressure curve, has not, we believe, been overestimated by

clinicians, and as before mentioned, in our systematic groups we have attempted insofar as practical, to eliminate those patients in whom this factor was likely to be a dominant one.

Gumprecht found a fall in the pressure of laboring men with readings between 160 and 200 mm., after rest in bed on their entrance into the hospital, and he attributes this drop to unaccustomed rest. Hensen,⁵ however, calls attention to the higher readings usual in patients of this class on the first day of their hospital residence. We are inclined from our studies to agree with Hensen, for we have not found that rest *per se*, that is, physical rest, materially alters either super- or normal blood-pressure, although it exerts a profound elevating influence on the low pressures of exhaustion. Concerning mental or psychic rest or sedation, however, we are strongly of the opinion that profound changes in pressure occur, and although we have not as yet proved it to our complete satisfaction, we believe that these factors determine to a very large degree the undoubted benefit derived from rest in cases of high pressure.

It is admittedly foreign to the nature and intent of this paper to enter into an attempt at physiological interpretation of the fall of blood-pressure after sleep, but the subject is so alluring and admits of so very many interesting and possibly therapeutically important inferences that it is difficult totally to abstain in this direction. From a somewhat limited number of observations conducted alike on high, medium and low pressure cases, it seems that the fall in pressure after sleep is much more pronounced after the customary regular or rhythmic sleep, be this night or day, while the drop which also occurs as a result of the sleep taken at irregular intervals is usually much less in degree and less abrupt in appearance, although we have some evidence to the effect that after profound physical exhaustion the drop in pressure which occurs with sleep is even more rapid, but it does not fall much if any below the accustomed level which we believe from these clinical cases to be an *individual period*, comparable to the usual pulse-rate in any given individual, though apparently quite classifiable with similar instances in the same type of persons.

That the drop is in some way directly connected with the phenomena of sleep is apparently suggested by the fact that in our groups, when the patients were not allowed to sleep, the pronounced fall does not take place although a certain drop occurs perhaps as a result of posture or rest. This conclusion is based on a study of sixty cases. Furthermore, when sleep is disturbed, as by disagreeable dreams, noise or pain, although complete unconsciousness may be attained the drop is not so pronounced. This fact may very likely account for the comparative exhaustion which

5. Quoted by Theodore Janeway: "A Clinical Study of Blood-Pressure."

is clinically observable in patients after a night of disturbed, although unconscious, sleep. This fact was especially suggested by one night's observations when the sleep in the general ward had been disturbed by the presence of a delirious patient. Records taken of previously studied patients, who despite the annoyance had become unconscious, showed a drop, but not to the accustomed degree.

Disturbance of patients during the first sleep delays, but does not necessarily prevent the maximum fall in pressure, but frequent interruption of sleep does prevent it. When the maximum drop has taken place before the patient wakes it does not recur that night no matter how sound the subsequent sleep may be.

As to whether this drop is occasioned by the sleep or whether it occurs as a rhythmic phenomenon, independent of, but concurrent with sleep, we do not as yet feel entirely prepared to speak, but we do not think from our studies that it is in any way concerned in the causation of sleep, for the fall appears subsequent to, rather than preliminary to, or concurrent with sound sleep. As some of our instances apparently show, sleep, sound, refreshing, at the usual time and apparently entirely physiological, may occur without this drop; we are nevertheless convinced that in general the drop is a physiological necessity and that its degree is determined in at least a general way by the requisite rest and release from tension demanded by the individual.

The amount of night urinary secretion is apparently in no way dependent on the grade or degree of pressure-drop in so far as can be determined from these cases. (Six cases only were studied in regard to this point, two high, two medium and two low.)

In an attempt to apply these observations clinically we have endeavored to ascertain whether prolonged sleep causes a proportionate lowering of the pressure. Within an ordinary degree at least this does not appear to be the case and attempts to secure even a temporarily lower twenty-four-hour pressure by prolonging or deepening the sleep were apparently without avail. Furthermore, we found that little difference existed in the total twenty-four-hour pressure whether the patient is confined to bed or is allowed to be up and about.

A special series of observations (ten instances) were conducted to determine whether the sleep drop might not be artificially increased in order to secure a lower pressure curve in concrete cases of high pressure. We obtained no results in this direction, and in cases in which the drop and curve had been previously determined, by the administration of potassium bromid in a dosage of as high as 120 grains the degree or persistence of the fall was not increased. The same lack of result was shown when chloral hydrate in a dosage of 50 grains per night was given,

yet the drop and curve were not materially altered. From these and from other clinical observations we feel justified in the discouraging conclusion that this sleep-drop cannot as yet be utilized therapeutically to lower the blood-pressure and that although its effect in high blood-pressure cases is more marked than that of any drug in medicinal doses, it cannot be employed therapeutically. It may, however, be said parenthetically that the more we study this question of blood-pressure the more we become persuaded toward the conclusion that the often frantic efforts to lower high blood-pressure are perhaps as harmful, if successful, as they are usually futile.

44 West Ninth Street.—84 West Twelfth Street.

ARTERIAL LESIONS FOUND IN PERSONS DYING FROM
ACUTE INFECTIONS, AND ATTEMPTS TO PRO-
DUCE ARTERIAL LESIONS IN ANIMALS
BY NON-INFECTIOUS TOXINS *

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In a former study¹ it was shown that diffuse arterial lesions of a mild grade were frequently associated with certain acute infectious diseases in young people. These lesions were in no way characteristic of acute infections, as they were similar to the usual lesions found in the arteries in old age, whatever be their causes. These lesions consisted of fatty changes with or without cellular invasion in the intima and media of the vessels. In some cases the connective tissue was increased in the intima, media or both, and in some there was loss of muscle substance in the media. In the arteries in the spleen there was a peculiar hyaline-like degeneration involving one or all the coats. It is impossible to say, therefore, whether or not these lesions in these special cases are due to the toxins of the disease.

In one of the cases of general septicemia in this former study a different kind of arterial lesion was found in the kidney. There was necrosis of the vessel wall with fibrin formation and invasion into and around the vessel wall of polynuclear leukocytes and endothelial cells, as is shown in the accompanying photograph.

It is known that the tubercle bacilli and the spirochetes of syphilis invade arterial walls and cause lesions characteristic of the organism, which leave a permanent scar. The question therefore arose as to the possibility of this lesion being due to the presence of some special infectious organism, or to a certain kind of circulating toxin.

This study consisted of a search for lesions of this type. For this purpose autopsy material, preserved in the usual routine manner of the Boston City Hospital pathological laboratory, was used. The tissue after Zenker's fixation was stained with eosin and methylene-blue stains. Sections from the more important organs and aorta were examined. Occasionally one or more organs were missing in a given case. Usually only one or two slides of the same organ were examined. This was found later

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*From the laboratory of the Department of Theory and Practice of Physic, Harvard University.

1. Frothingham: THE ARCHIVES INT. MED., 1911, viii, 153.

to have been unfortunate as in some cases lesions would only appear in every third or fourth slide.

As this type of injury to the vessel wall was quite distinct from the early or late so-called arteriosclerotic changes, tissue from patients up to 40 years of age was studied. In all, sections from fifty-six patients were examined. Of these forty-eight died from acute infectious diseases. These forty-eight cases included bronchopneumonia, diphtheria, typhoid fever, pneumonia, tuberculosis, scarlatina, measles, general sepsis, and septic conditions of the ear, salpinx, peritoneum, meninges, joints, brain, liver and pleura.

No mention will be made of the lesions in the vessels characteristic of so-called arteriosclerosis and occurring in cases of acute infection as described above. Only those lesions are mentioned in which there was necrosis of the vessel wall with fibrin formation and cellular invasion. In some of these vessels thrombi were formed which extended beyond the site of the necrosis. In none of the eight cases which died from chronic non-infectious disorders were lesions of this type found.

Of the forty-eight cases with acute infections eight showed arterial lesions of this type. These cases with the location of the lesions were as follows:

Artery in the kidney from the case numbered Path. Records 1910-15. For this photograph I am indebted to Dr. F. B. Mallory.

Pathological record B. C. H. 1911-47, aged 6 years. Purulent meningitis. Autopsy cultures, streptococcus. Arteries in meninges involved. Arteries in other organs not affected.

Path. record B. C. H. 1911-38, aged 32 years, tuberculosis of lung and meninges. Autopsy cultures, tubercle bacilli, and mixed growth. Only meningeal vessels show this lesion.

Path. record B. C. H. 1911-42, aged 34 years. Acute endocarditis, pneumonia, pulmonary infarcts. No culture taken. This type of arterial lesion occurred only in the lung.

Path. record B. C. H. 1911-4, aged 2 years. Empyema and lung abscess with miliary tuberculosis following scarlet fever. Autopsy cultures showed mixed infection. Acute arterial lesions of this type found in liver and lungs.

Path. record 1910-179, aged 3 years. Empyema, pericarditis, and meningitis following diphtheria. Autopsy cultures negative. This type of lesion only found in the vessels of the lung and meninges.

Path. record 1911-96, aged 3 years. Diphtheria and bronchopneumonia. Autopsy cultures, diphtheria bacilli and others. Vessels in the pharyngeal wall showed these lesions.

Path. record 1910-15, aged 8 years. General sepsis with pus in joints, etc., following scarlet fever. No cultures taken. Marked arterial lesions of this type were found in the kidney, heart, liver, and muscle abscess.

Path. record, 1897-171, aged 3 years. Diphtheria and interstitial nephritis. Autopsy cultures streptococcus and staphylococcus. Only tissue of the kidney was available. In the kidney were marked arterial lesions of this acute type.

From a study of these cases it is evident that marked arterial lesions of this type, although not common, do occur with moderate frequency, and are pretty well distributed throughout the different organs. They

seem to occur chiefly in infections caused by or complicated with the pus-forming cocci. In no case could the possibility of the bacteria being present in the lesion be excluded, although they were not demonstrated. The case of periarteritis nodosa reported by Longcope² shows a similar lesion and is considered to be due to some infectious process. Recently Mallory³ has found similar lesions in the arteries of the heart during acute articular rheumatism. The end-result of such a lesion on healing must show a permanent scar in the arterial wall. It seems reasonable



Marked arterial lesion found in an artery in the kidney following scarlet fever.

to suppose that less severe infections of the same type which terminate in recovery may cause similar arterial lesions with an arterial scar carried into later life. The question immediately arises, Do repeated lesions of this sort lead to the so-called arteriosclerosis of old age? If such a lesion heals with a partial occlusion of the lumen, it is reasonable to

2. Longcope: Bull. Ayer Clin. Lab., Penn. Hosp., December, 1908.

3. Mallory, F. B.: Unpublished article.

suppose that the vessel wall distal to this point may suffer from diminished blood-supply. It is also possible that the arterial wall adjacent to the scar may suffer from lack of nutrition due to the surrounding scar tissue.

With the hope that clinical histories might throw some light on the cause of arteriosclerosis the record of two patients with marked sclerosis of the arteries aged 22 and 16 years, respectively, were carefully studied. There was nothing in the history of either case which could be pointed to as a possible cause of the sclerosis. It is only fair to state that the histories were not carefully taken with this point in view.

In studying these sections it was noted that in cases of chronic disorder such as nephritis, diabetes, etc., the arterial lesions characteristic of arteriosclerosis were usually quite marked. An attempt was made, therefore, to produce in rabbits arterial lesions of the degenerative type by metabolic or chemical poisons.

Although the experiments were uniformly unsuccessful in producing lesions, they will be briefly described. In this work tissues, preserved in formaldehyd solution, were stained with Scharlach R for fat in addition to the routine eosin and methylene-blue stain on Zenker fixed material used in this laboratory.

Double nephrectomy under ether anesthesia was performed on five rabbits which lived from twenty-four to forty-four hours after operation. In this time fatty changes had occurred in the heart muscle as described by Lewis,⁴ but no evidence was found of lesions in the arteries.

Bovine⁵ bile was injected intravenously, intraperitoneally and subcutaneously in varying amounts into rabbits for different lengths of time. Although the results varied with the different biles used it seemed as though fatty changes were produced in the heart and liver in some cases. No arterial lesions were formed, however, in any of the cases. Tissue from a cat which had been kept in a state of glycosuria for over a year by Dr. Allen was examined for fatty changes in the vessels. No pieces of the aorta were obtainable, but the arteries in the different organs showed no degenerative lesions.

The kidneys were examined in four rabbits which had been injected by Dr. Christian⁶ with uranium nitrate or either caffeine or adrenalin and spartein in work on experimental nephritis. In these kidneys marked lesions were found in the parenchymal cells and also in the glomeruli. Hemorrhages were present in the glomeruli. In three of these cases no arterial lesions were found. In one a few fat granules were present in a few of the small arteries.

4. Lewis: Jour. Med. Research, 1907, xvii, 291.

5. Frothingham and Minot: Jour. Med. Research, 1912, xxvii.

6. Christian, Smith and Walker: THE ARCHIVES INT. MED., 1911, viii, 468.

In three rabbits which had been injected with adrenalin and spartein by Dr. Christian there were marked degenerative lesions in the cardiac muscle and proliferation of the cardiac connective tissue. In these cases the arteries showed no lesion with the possible exception of a slight amount of fat in a few arteries in one case. It is interesting to note that toxins, which will produce an hypertrophy of connective tissue in the stroma of an organ, apparently have no effect on the connective tissue of the vessel walls.

CONCLUSION

Although this study has thrown no light on the relation between non-infectious toxins and arterial disease it has shown that during acute infectious diseases severe localized arterial lesions may occur.

51 Hereford Street.

SOME CLINICAL AND EXPERIMENTAL OBSERVATIONS WITH A SACCHAROMYCETE *

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INTRODUCTION

My object in presenting this paper is to relate the facts in connection with my observations and to call attention to the possible significance of yeast organisms in the sputa of doubtful lung cases.

I am greatly indebted to the physicians of Pomona who have so kindly and generously cooperated with me in these investigations, and to Dr. Charles C. Browning of Los Angeles for consultation and suggestions in Case 7; to Dr. D. J. Davis of St. Luke's Hospital, Chicago, for his interest and valuable suggestions, and also to Dr. I. C. Herb of the Rush Medical College for assistance in translation of literature. I desire to express my deep appreciation for the ever ready and helpful interest shown by Dr. Stanley P. Black of Pasadena, whose wise counsel and advice have been a constant incentive to careful work.

LITERATURE

Claude Bernard,¹ the French physiologist, experimenting with yeast in 1848, produced infections in animals. Since that time various observers have had similar results, using for their experiments wine yeasts, beer yeasts and the thrush fungus. Sanfelice,² experimenting in 1895 with two varieties of saccharomyces, one from fruit juice, found them to be pathogenic for guinea-pigs and white mice. Lydia Rabinowitch³ made a careful experimental study with forty yeasts which were obtained from different sources. She found eight pathogenic, some producing granulomatous nodules and others a septicemia. Maffucci and Sirleo⁴ found that a species of saccharomyces produced in guinea-pigs a pulmonary affection which resembled tuberculous pneumonia. Demme's⁵ *Saccharomyces ruber*, which he held responsible for an outbreak of intestinal catarrh in a family of seven children, was found to be pathogenic for guinea-pigs, dogs and mice.

That saccharomycosis of the mucous membrane is possible has been demonstrated by Colpe⁶ and Bosdike, who obtained a pathogenic yeast

*Manuscript submitted for publication May 24, 1912.

*Read at the meeting of the Southern California Medical Society at Pasadena, May 1, 1912.

1. Bernard, Claude: *Leçons de Pathologie Experimentale*, 1871.

2. Sanfelice, Francesco: *Centralbl. f. Bakteriöl.*, 1895, xviii, 52.

3. Rabinowitch, Lydia: *Ztschr. f. Hyg. u. Infektionskrankh.*, 1895, xxi.

4. Maffucci, A., and Sirleo, L.: *Policlinico*, 1895, p. 138.

5. Demme, R.: *Berlin* 1890, Hirschwald.

6. Colpe: *Arch. f. Gynäk.*, 1894, xlvii.

from a patient with chronic catarrh of the uterine cervix. Busse⁷ found the fungus in proliferative catarrh of the nasal mucosa. Busse also, in 1894, described a yeast which he found in a case of pyemia and which he named *Saccharomyces hominis*. In all he published four communications regarding this fungus, and the same organism was described by Buschke.⁸ Gilchrist⁹ described a pure skin disease caused by a yeastlike fungus. Curtis¹⁰ published an account of a case in which a yeast caused myxoma-like tumors. He called this fungus *Saccharomyces humaine*. Huebner¹¹ found a saccharomycete in pustules of the skin on various parts of the body. Corselli and Frisco¹² cite a case in which nodules were seen in omentum and mesentery. In this case yeast organisms were found in chylous and ascitic fluids obtained by exploratory puncture during

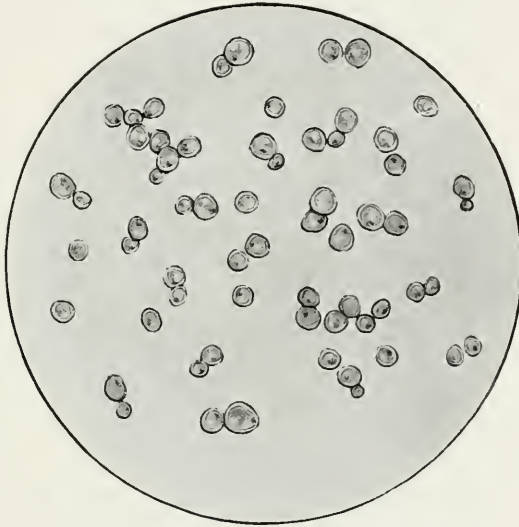


Fig. 1.—Saccharomycete in fresh drop. Oil immersion.

life, and were found to be pathogenic for guinea-pigs, rabbits and dogs. Troisième and Achalmé¹³ found a saccharomycete in a case of pseudo-membranous angina in a typhoid fever patient. Clinton Hickey¹⁴ of

7. Busse, Otto: Ueber Saccharomycosis hominis, Virchows Arch. f. path. Anat., 1895, exl, 23; Experim. Untersuch. über Saccharomycosis, Virchows Arch. f. path. Anat., 1896, cxliv, 369.

8. Buschke, A.: Klin. Vorträge, 1898, No. 218.

9. Gilchrist, T. C.: The Johns Hopkins Hosp. Rep., 1896, i, 269.

10. Curtis: Contribution à l'Etude de la Saccharomycose humaine, Ann. de l'Inst. Pasteur, 1896, x, 449.

11. Heubner: Deutsch. med. Wchnschr., 1904, Nos. 33 and 34.

12. Corselli, G., e Frisco, B.: Centralbl. f. Bakteriöl., 1895, xviii, 368.

13. Troissier, E., and Achalmé, P.: Arch. de méd. expéd. et d'anat. path., 1895, v, 29.

14. Hickey, Clinton: Colorado Med. Jour., 1900, vi, No. 2, p. 485.

Denver described in 1900 two cases of scarlatinal angina and one of "sore throat" in which a dense exudate covered tonsils, pillars of fauces and margins of soft palate. The city bacteriologist reported "no Klebs-Löffler bacilli, no streptococci, and no staphylococci, but numerous yeast cells." Steinhaus¹⁵ found a yeast in a child suffering from scarlet fever which he called *Saccharomyces membranogenus*. On the fifth day the



Fig. 2.—*Saccharomyces*, smear from 24-hour culture, stained with Löffler's methylene-blue. Oil immersion.

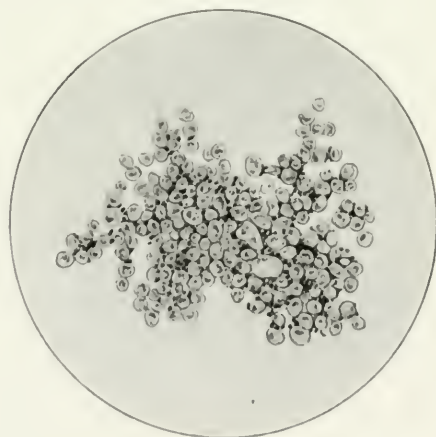


Fig. 3.—*Saccharomyces*, smear from 3-weeks old culture showing many empty capsules, stained with Löffler's methylene-blue. Oil immersion.

child developed croup with a very fetid odor. On the twenty-first day dyspnea developed and tracheotomy was performed. After operation the child coughed up a tenacious mass, following which breathing became

¹⁵ Steinhaus: *Centralbl. f. Bakteriol.*, 1 abt. Orig., 1906-07, xliii, part 1, p. 49.

easier. An aseptic instrument was passed into the trachea and membrane secured for cultures. One thousand units of antitoxin were given, as diphtheria had been diagnosed. The patient died next day. Autopsy was not allowed. Cultures were made on Löffler's blood-serum. Sixteen hours later the plate showed large, glistening, round, light yellow-tinged colonies which, much to his surprise, revealed pure cultures of yeast.

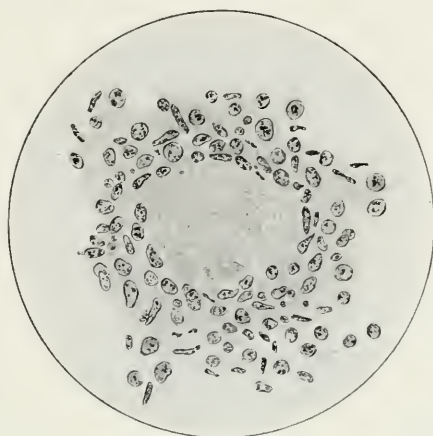


Fig. 4.—Saccharomycete in tissues, surrounded by leukocytes, mostly polynuclears; hematoxylin and eosin stain. Oil immersion.

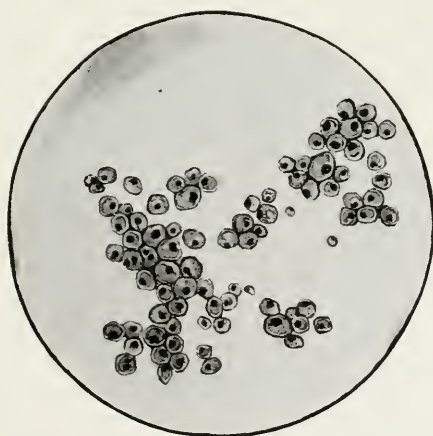


Fig. 5.—Saccharomycete, nuclear stain, Janssen's and Leblanc's modification of Mueller's method. Oil immersion.

In his animal experiments, mice, guinea-pigs and rabbits were employed. He used intravenous, subcutaneous and abdominal injections; also feeding bread soaked in bouillon cultures of yeast, all of which produced the characteristic infection, and at autopsy the characteristic miliary tubercles

and sections revealed the yeast fungus in all organs and in blood-vessels and nerves. His article is complete in every detail. Reitman¹⁶ cites a case, a patient of 30 years, sick eleven days, who died four days after entrance to the hospital. The autopsy showed croupous pneumonia and glomerulitis. Only sections of kidneys were examined, but many of these sections contained double-contoured refractile bodies between 5 and 20 microns found in epithelium of the tubules in the glomeruli, and free in the blood-stream. It was impossible to make cultures in this case on account of the non-recognition before hardening. He depended on staining and morphology, but thinks that they correspond to the organism described by Busse. Castellani,¹⁷ director of the Clinic for Tropical Diseases, Colombo, gives some interesting observations on fungi found

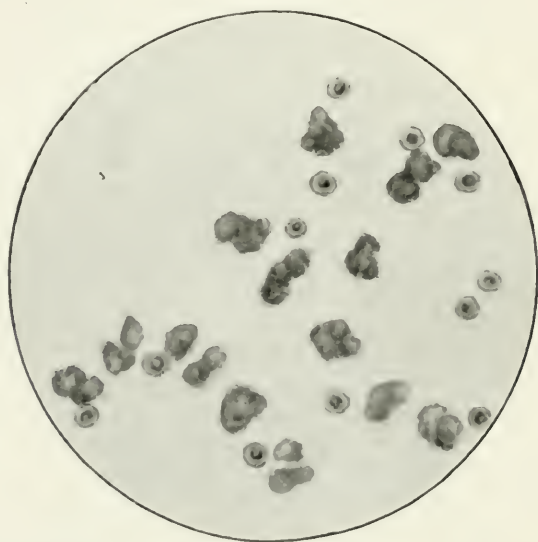


Fig. 6.—*Saccharomyces*; smear from pus in Case 14; nuclear stain for differentiating. Oil immersion.

in tropical bronchomycoses, to which various names are given (tea-factory cough, copra cough, etc.). Among other fungi he found a *saccharomyces* twice.

The subject of pathogenic yeasts has been so carefully and thoroughly covered, and the literature so completely reviewed by Ricketts in his monograph "*Oidiomycosis (Blastomycosis) of the Skin and Its Fungi*," and by Hektoen, in his summary of cases of "*Systemic Blastomycosis and Coccidioidal Granulomata*," that further reference except to these two

16. Reitman: *Centralbl. f. Bakteriol.*, 1895, p. 225.

17. Castellani, Aldo: Observations on the Fungi found in the Tropical Bronchomycoses, *Lancet*, London, 1912, i, No. 1, p. 13.

works, with their bibliography, seems unnecessary. Hektoen¹⁸ says that the history of many of the cases cited by him, and the bronchopneumonic character of some, may be taken to indicate their air-borne nature. In a number of these cases blastomycetes were found in the sputum, and in some of them the pulmonary symptoms were the first to appear, followed in most cases by localization of lesions.

Regarding the occurrence of yeasts in Nature, Klocker¹⁹ says:

"Hansen's researches on the circulation of saccharomycetes in Nature, and on the amount of microorganisms in the air at various seasons of the year, have led to the following results, very important to the brewer: (1) Wind and insects are the most important means of transportation of yeast cells in Nature, especially the first. (2) Dust clouds in the harvest months are rich in strong yeast cells produced on sweet, juicy fruits." He describes saccharomycetes as "single cell fungi in which vegetative increase takes place by budding and which develop endospores in their interior under certain conditions; sometimes they may form typical mycelium. The various related species are grouped according to their action on various sugars."

In a careful comparative study of other known cells, together with the yeast plants, Mutchler came to the following conclusions which he thought justifiable: (1) Yeast-cells contain structural elements that are homologous with the structural elements of the cells of higher plants and with the known structural elements of animal cells and with the structural elements of the bacteria and the cyanophyceæ as worked out by Butchle and also by Kumbler. (2) The structural elements consist of four definite regions, are found in both mature cells and in the growing buds and correspond to what is well known in the higher plants and in animal cells as cytoplasm, nuclear membrane, nucleus and nucleolus. The structural elements may be demonstrated clearly by the four methods of differential staining discussed by him and are to be found in every yeast cell. Emerson²⁰ says that as the presence in the sputum of certain pathogenic yeasts cannot be denied, in doubtful cases they should be looked for as a possible explanation of anomalous lung conditions. Hektoen suggests further careful study of new cases both clinically and anatomically, and further observations in regard to the blood, especially to the number of leukocytes and differential counts. B. F. Davis²¹ of Chicago has given valuable information in immunological reactions of *oidiomycosis*.

18. Hektoen, Ludvig: *Jour. Am. Med. Assn.*, 1907, xlix, 1071.

19. Klocker: "Fermentation organisms," 1903. English translation of the German edition, p. 248.

20. Emerson, Chas. P.: *Clinical Diagnosis*, 1911.

21. Davis, B. F.: *Jour. Infect. Dis.*, 1911, viii, 190.

AUTHOR'S OBSERVATIONS OF A YEAST

During more than two years of clinical laboratory work in Pomona I have encountered a yeast in fifteen individuals sent to me for laboratory diagnosis. This organism I first discovered in a vaginal discharge. Four months later I found similar organisms in the sputum of a child said to have tuberculosis, and again in a culture from the tonsil membrane of a child supposed to be suffering from diphtheria. The fourth time I encountered this fungus was in the sputum of a patient with a pulmonary lesion resembling lobar pneumonia in the early stage of resolution. In this case repeated examinations of the sputum failed to reveal any tubercle bacilli and the tuberculin test was negative. To ascertain what was causing the symptoms I made cultures from the sputum and each time got a pure growth of an organism which I identified as a saccharomycete and which gave the same results culturally and with animal experimentation as did the fungus found in the vaginal discharge in the first case.

After the above experience I made a routine practice of washing and examining culturally all sputa sent to the laboratory in which, after repeated examinations, I found no tubercle bacilli. As a result I have discovered a yeast organism in a number of other patients which corresponds morphologically and culturally to those found in the preceding cases. At times the organism was found in pure culture, again in connection with a staphylococcus or *Micrococcus catarrhalis*, and twice it was found mixed with tubercle bacilli, but in all cases the morphological and cultural characteristics were identical, and animal experiments with the strains tested gave the same results.

Morphology.—This organism resembles the *Saccharomyces cerevisiae* both culturally and morphologically, but the latter on all culture media grows less profusely and is less spherical. It is about the size of a red blood-corpuscle, possesses a double-contoured capsule and contains fine granules and refractile bodies like fat or vacuoles. Old cultures show lessening of granules and extension of vacuoles, and numerous empty capsules. It grows by budding and possesses a nucleus which can be demonstrated by special staining. In one old culture there was a slight tendency to form threads. I have found no endospores but have made no special cultures for spore formation.

Staining Properties.—In smears from cultures this organism stains well with all ordinary dyes. It is Gram positive. It is not acid fast. Direct smears from pus or thin sputum are best treated with Wright's blood stain, which colors the pus cells a pinkish purple and the yeast organisms a dark blue, while the red blood-cells are a brick red. For staining the nucleus I have used Janssen's and Leblanc's modification of Mueller's method as used by brewers, the technic of which is given in "Klocker's Fermentation Organisms." This requires four days but is

excellent for differential purposes. It stains the nucleus a dark red and the cytoplasm a pale pink.

Cultural Characteristics.—On glucose and glycerin-agar slants there is a profuse creamy growth at 37 C. in twelve to twenty-four hours. On potato slants but a slight film in the same length of time. It turns litmus milk a full creamy white in twenty-four hours with formation of a soft curd. It grows vigorously on both plain and glucose bouillon, forming a heavy sediment in the bottom of the tubes, and in the latter the appearance of foam on shaking. There is a profuse growth on both plum and grape decoctions but no foam on shaking the tubes. It does not liquefy gelatin, but growth appears along the line of the stab with roseate formation at the top. Agar plates reveal white moist points in twenty-four hours. On all culture media there is but slight growth at room temperature. The minimum temperature for visible growth of this organism is 18 C. and the maximum temperature is 69 C. It is devitalized at 71 C. for one hour. Two-year-old cultures which were quite dry were moistened with salt solution, and from them fresh culture media inoculated. A fairly vigorous growth resulted. Glucose is fermented, giving rise to alcohol and carbon dioxide. Growth occurs in lactose, dextrose, raffinose, inulin and mannite in 2 per cent. solution, though there is no evidence of fermentation. On all culture media this organism gives rise to the characteristic odor of yeast. Plates continually exposed in the laboratory reveal no growth of this fungus.

Animal Experiments.—This organism is pathogenic for rabbits, white rats, guinea-pigs and monkeys. Subcutaneous injections produce slowly developing septic conditions from which the animals tend to recover if not injected too often. Intraperitoneal injections produce in guinea-pigs and white rats a rapidly fatal septicemia; in rabbits and monkeys within a few weeks rapid loss of weight and more slowly developing septicemia. In all animals within a few hours after intraperitoneal injections there is rapid breathing, high temperature and some leukocytosis with slight increase of mononuclear cells. Autopsies without exception reveal grayish miliary tubercles thickly studding all internal organs, and peritoneal and pericardial surfaces. Sections of these tubercles show masses of the yeast-cells, surrounded by leukocytes, mostly polynuclears. The organism was recovered in pure culture from the heart's blood, bile, peritoneal and pericardial fluids and the miliary tubercles, and direct smears showed full-grown and budding yeast cells.

HISTORIES OF CASES IN WHICH THE ORGANISM OCCURRED

CASE 1.—Physician, Dr. Huntington; patient, J. H., aged 11. The patient came under observation Dec. 4, 1909. Four months previously while swinging on a rope she lost her hold and slid down to the knotted end, receiving injuries about

the external genitals. When first seen the labia were red, smooth, shining and sore, small whitish patches thickly covering the parts. These lesions which, when first seen, were confined to the external genitals, later invaded the vaginal tract. The whitish patches rapidly coalesced and formed a clinging membrane, and if not treated frequently the underlying parts became highly inflamed and very sore. When daily treatments were given, cultures showed feeble growth; but if three or four days elapsed between treatments, cultures yielded vigorous growth. From December, 1909, until March, 1910, daily and often twice daily treatments were given. From March until July laboratory examinations were continued at intervals, but during this period there was no reappearance of the patches, or growth on culture media, although the parts remained red and shining. In July the characteristic whitish patches were again observed on the inflamed parts and a culture taken revealed a profuse growth of the yeast in twelve hours. It was a problem to find a solution of anything strong enough to affect the growth without irritating the mucous membrane. Weak solutions of mercury chlorid, copper sulphate, ichthyol and boric acid all caused pain. Various powders proved inefficient. Cleaning the parts with sterile water, using gentle friction, gave best results. Douching the parts with sterile water without friction had no effect. The patient had little systemic affection. The cervical glands were slightly enlarged, but there was no elevation of temperature; the patient gained in weight during the treatments. Late in July the family removed to Oregon and two months later the father of the child reported that there was no further trouble.

CASE 2.—Physician, Dr. Toland; patient, a 4-year-old son of Mrs. T. The mother in April, 1910, consulted Dr. Toland about the child, who was coughing excessively. This case had been pronounced tuberculosis by her former physician. In the sputum sent to the laboratory for examination I found a yeast, but no tubercle bacilli. The mother left town soon afterward and the child was not heard from again until December, 1911. The cough was still present, but the child had improved physically.

CASE 3.—Physician, Dr. Toland; patient, W. M. S., business man, aged 36. The patient came under notice in 1910 with pharyngitis. He had lost in weight slightly and feared tuberculosis. The tuberculin test was negative; repeated examinations of sputum covering a period of several months failed to reveal tubercle bacilli. Cultures from sputum yielded pure growth of a yeast. The cough continued to be troublesome for more than a year but by November, 1911, it had entirely disappeared.

CASE 4.—Physician, Dr. Savage; patient, a girl of 10 years, with a history of chronic enlargement of the tonsils for two years, which, when first seen, were soft and boggy, associated with acute inflammation of the entire throat, and dense yellow patches confined to the tonsils. From a detached piece of membrane sent to the laboratory a culture revealed a vigorous growth of a yeast but no Klebs-Löffler bacilli. While waiting for the laboratory diagnosis antitoxin was given, but the membrane continued to form and three weeks later intubation was performed. The child made a good recovery.

CASE 5.—Physician, Dr. Swindt; patient, Mr. H. V. S., aged 56, a rancher. This patient was first seen in June, 1910. Two weeks before coming under notice he had a severe "cold" and cough, with viscid, blood-streaked sputum. At the time of entrance to the hospital he had chills, sweats and a temperature of 102 F. At the base of the left lung were detected signs of lobar pneumonia undergoing resolution. The blood and urine were normal. The tuberculin test was negative, and frequent examinations of the sputum revealed no tubercle bacilli, but cultures from the sputum resulted in a pure growth of a yeast. Large doses of sodium iodid were given and within two weeks the pulmonary symptoms had entirely disappeared. Phlebitis of the left leg occurred while in the hospital, and lasted for about three weeks. The patient reported, Jan. 15, 1912, that there was no cough or other pulmonary symptoms. The left leg swelled some when he worked hard.

CASE 6.—Patient, M. H., servant girl, aged 22. This patient was sent directly to the laboratory for a sputum examination by her employer, on account of a constant cough. She had come to California during the early summer on account of "catarrh." Her general health improved but the cough persisted. Repeated examinations of sputum failed to reveal tubercle bacilli. The tuberculin test was negative and the blood was normal. Cultures from the sputum yielded an almost pure growth of a yeast. Her employer advised her to seek another position and she took service in a mountain resort, but the high altitude did not agree with her and she went to Long Beach. Information from her first employer in November, 1911, was that she had entirely recovered.

CASE 7.—Physician, Dr. Browning; patient, Mrs. E. D. C., aged 35, married. The patient came from Idaho to southern California on account of persistent cough which dated from an attack of bronchitis in March, 1910, from which time she complained of a pressure over the chest and a difficulty in breathing. She had a loose paroxysmal cough with a profuse mucopurulent expectoration which was discharged after violent effort. There was a moderate degree of emaciation. Temperature was 99 F., pulse 100. The appetite was good and the digestion fair. The right side of the chest was normal, with dulness over entire left chest and especially pronounced over the third rib. Sputum examinations at intervals of from two to four days from January until May, 1911, failed to reveal tubercle bacilli. The tuberculin test was negative. Frequent cultures from the sputum always yielded a pure growth of a yeast and in a blood culture (bouillon) the same organism was found. Autobacterins of the yeast were given at seven-day intervals for six weeks, also various preparations of the iodids. The patient gained in weight and improved markedly, and in cultures from the sputum the growth of the yeast organism gradually disappeared. April 23 she took a long auto ride, during which she became overtired and thoroughly chilled. This resulted in an elevation of temperature (104 F.) and great prostration, and thereafter tubercle bacilli were observed in every specimen of sputum examined. As soon as the patient was able to travel again she went east and died six months later.

CASE 8.—Physician, Dr. Davis; patient, Miss V. H., aged 19, a student. In June, 1909, this patient came under observation with a laryngitis which did not yield to treatment. Examination of the lungs revealed a small area of infiltration, in which occasional moist râles were heard, just external to left sternoclavicular articulation. The morning temperature ranged from 96.6 F. to 100.2 F. Afternoon temperature ranged from 101 F. to 104 F. There was a troublesome cough and a profuse expectoration; also gradual loss of weight and night sweats. In November, 1909, a sputum examination revealed tubercle bacilli mixed with pus organisms. Tuberculin was not given until December, 1910, from which time this treatment was continued until March, 1911, but the temperature remained high and the patient was losing ground. At this time the sputum was sent to my laboratory with a view of having an autobacterin prepared for the mixed infection. Sputum examinations revealed very few tubercle bacilli. Cultures revealed a luxuriant growth of a yeast, with *Staphylococcus aureus*. The tuberculin was discontinued and an autobacterin of the yeast organism given every seven days for six weeks. The afternoon temperature gradually but steadily decreased but never at any time became normal. During the same time the yeast growth decreased until there was scarcely anything visible on culture media in twenty-four hours. The patient's general health, however, did not improve and she died May 29, 1911. There was no autopsy.

CASE 9.—Patient, Miss V. R., school girl, aged 16. This patient was almost a constant companion of the 16-year-old daughter of the patient, Case 7. She was sent directly to the laboratory by her mother for a sputum examination because of a constant, distressing cough. A sputum examination revealed no tubercle bacilli and the tuberculin test was negative. In a culture from the sputum pure growth of a yeast resulted. Potassium iodid, 10 grains three times daily, caused the cough to disappear entirely within a few weeks.

CASE 10.—Patient, Mrs. R., seamstress, aged 51, mother of patient Case 9, developed a cough soon after the daughter. All of the findings were exactly as in Case 9, but the cough was more persistent and she was obliged to keep up the iodids longer and in much larger doses. Eight months later both patients were entirely well.

CASE 11.—Physician, Dr. Swindt; patient, Mr. C. H. A., clerk, aged 55. This patient had a chronic bronchitis for thirty years, but his general health was good up to five years previous to examination. During the previous five years he had occasional fever and frequent attacks of hemoptysis, but never any marked loss of weight. He had profuse fetid expectorations for the previous four years. There were signs of chronic bronchitis in both lungs. The fetor disappeared under sodium iodid, and creosote reduced the amount of expectoration. In April, 1911, a blood examination was negative, a tuberculin test negative and there were no tubercle bacilli found. A culture from the sputum revealed a yeast with *Staphylococcus albus*. An autobacterin of the yeast organism caused an exacerbation of symptoms which alarmed the patient and the dose was not repeated. Patient went east in May of the same year. A few months later he reported that he was taking *staphylococcus-vaccine* (stock) without improvement. This patient had frequent sputum examinations during the past five years and tubercle bacilli were never found. An unidentified organism, however, had been reported once.

CASE 12.—Physician, Dr. Swindt; patient, Mrs. J. B. P., aged 67. This patient had chronic cough for many years. During the previous four years she suffered greatly from paroxysms resembling pertussis. Her general health was good. Both lungs showed signs of moderate bronchitis. No tubercle bacilli, but pure culture of a yeast from the sputum. The paroxysms were completely relieved and the cough reduced to a minimum in about three weeks by the use of sodium iodid in large doses.

CASE 13.—Physician, Dr. Gareclon; patient, W. S., aged 47. This patient was in the hospital with typhoid fever, and in a culture from the feces, in connection with the typhoid bacilli, a yeast was found. The patient died after a two months' illness. No autopsy. As this yeast organism resembled all of the preceding ones morphologically and culturally, animal experiments were undertaken with it, and the same results obtained as in the previous cases. It was also identified as a *saccharomycete*.

CASE 14.—Physicians, Dr. Huntington, Dr. Swindt; patient, Miss L. T., aged 35. The patient came under observation in November, 1910. She had had arthritis deformans for ten years and the spine and large joints were stiff. Four years previously she had appendicitis, but no operation. Three years previously she had pleurisy with effusion, followed by empyema and evacuation through the left bronchus. Since then there had been a constant, profuse expectoration. At intervals of three to eight weeks there would be an enormous increase of this expectoration, when, in a short time, from 1 to 3 pints of stinking pus would evacuate through the bronchus, pouring through nose and mouth and almost strangling the patient. In February, 1911, a sputum examination revealed no tubercle bacilli, but a culture showed a yeast, together with *Staphylococcus albus* and *M. catarrhalis*. Nov. 7, 1911, a sputum examination gave the same results as ten months previously, but with an increase of the yeast organism. The tuberculin test was negative; there was some leukocytosis with 82 per cent. polymorphonuclears. The temperature ranged from subnormal to 103 F.; pulse from 90 to 120; respiration from 18 to 26. A radiograph showed a shadow on the left side below the clavicle. November 11 the seventh and eighth ribs on the left side were resected and over 3 pints of pus removed. The lung was found in a small, contracted mass high up in the cavity, with apparent communication with the bronchus. The condition of the patient did not permit of decortication. The cough disappeared and the general condition immensely improved following the evacuation of pus. In smears from the pus from the wound yeast organisms were found. Culture from the pus revealed yeast organisms in almost pure growth. An

agglutination test of the yeast with this patient's serum, 1-40 and 1-50, was strongly positive, while controls were negative. An extract of yeast made for me in the Cutter Laboratory, Berkeley, according to the technic for Koch's old tuberculin, proved slightly positive in a skin test, controls negative. Autobacterins of the yeast were begun a few weeks after the patient left the hospital and her improvement has been uninterrupted.

CASE 15.—Physician, Dr. Kelly. The patient, Miss A. C., aged 15, school girl, had always been subject to "colds." She came under notice in December, 1911, with a severe cough. The mother of the child said that cough and expectoration had been continuous for the previous three months. There was some loss of weight and some anemia. The temperature was 99 F., pulse 90; blood examination showed hemoglobin 50 per cent., red blood-cells 80 per cent., no leukocytosis, polynuclears 83 per cent.; tuberculin test negative. An examination of the sputum every day for two weeks revealed no tubercle bacilli. A culture from the sputum showed a vigorous growth of a yeast with *Staphylococcus aureus*. An agglutination test with the yeast was slightly positive, controls negative. The patient refused to have a skin test with the yeast extract. Large doses of sodium iodid were given.

The above histories are not complete, but abstracts as given me by the physicians in whose service they occurred.

NOTES ON CASES

In few of the cases herein cited have we had opportunity for careful clinical study. Only two of the patients were in the hospital at all and then for only a short time. The organisms from Cases 1, 4, 5, 7, 8, 13, 14 and 15 were employed in animal experiments with practically the same results. In Case 1 we were not allowed to make a skin test or blood examinations, but the clinical picture was observed closely. In taking smears or cultures here, the parts were always cleansed first with sterile water. It was significant that with the disappearance of the yeast fungus in this case the trouble disappeared entirely. Case 2 we had on opportunity of observing. Case 4 suggests cases cited by Hickey and Steinhaus in the literature, inasmuch as a tenacious membrane formed and reformed, and that there was an absence of the Klebs-Löffler bacillus. As Case 5 was in the hospital I made frequent blood and sputum examinations, but at that time had not begun making the skin and agglutination tests with the yeast. However, the absence of any organism except this fungus suggested the iodids. There was no opportunity to observe Case 6 after the laboratory analysis and it was only through the kindness of her first employer that we learned of her present condition. In Cases 7 and 8 tubercle bacilli were found mixed with the yeast organisms, but it would seem to be a secondary invader in the former, while probably in the latter the tuberculous infection was primary. Both of these patients died, but as there was no autopsy in either case, there can be no definite knowledge regarding this. It is, however, significant that both of these patients were benefited by autobacterins and iodids. The facts in Cases 9 and 10 suggest that this organism may be transferred

from one person to another. The suspension of yeast organisms prepared for Case 11 was kept at a temperature of 70 C. for one hour, as the previous ones for Cases 7 and 8 had been, and as a twenty-four-hour culture taken from this emulsion was sterile, the dose was then given. After forty-eight hours, however, the culture tube revealed a slight growth of yeast. This undoubtedly accounted for the exacerbation of his symptoms.

Case 12 was remarkable in that it was an unmixed infection of yeast, and that it was so quickly and entirely relieved by the iodids. Case 13 was not observed with regard to the yeast organism found. We isolated and identified it simply because it resembled the organisms previously identified as *saccharomycetes*. We had more opportunity for careful study of Case 14, and the observations were fairly satisfactory. The very positive agglutination test, the slightly positive skin reaction, together with the occurrence of the same organism in the pus from the wound that I had previously and repeatedly found in the sputum, are suggestive of the pathogenicity of the *saccharomycete* in this case. Case 15 had only begun to improve with the iodids when she began taking a patent medicine and was lost sight of. In all of these cases the physicians have remarked the unusual fetor and viscid character of the sputum and repeated attacks of "colds."

The examination of the sputum requires some care. It should be washed in normal or tenth-normal sodium or potassium hydrate, and cultures made from the parts resembling pus. Smears should be treated as described above. If the sputum is to be examined unstained it should be covered with a normal solution of sodium or potassium hydrate, and allowed to stand for at least thirty minutes to dissolve the mucus. The yeast cells being resistant to the action of the alkali can easily be found and are not confused with red blood-cells.

This report leaves much to be desired in the way of clinical observation of cases, and autopsy records in cases of death; also blood examinations, especially in cases in which the *saccharomycete* is the only organism found. The complement deviation test should also be made in connection with the agglutination and skin tests. Animals should be immunized and agglutination tests made with their sera.

Five other patients are still under observation in whom a yeast has been found. One is a child aged 4½ years with repeated attacks of bronchitis followed by asthma. It has been impossible thus far to secure a satisfactory specimen of sputum, as she swallows it, but a yeast has been found in a blood culture (agar plate), also in a culture from the feces during one of her attacks of bronchitis, and her serum agglutinates the yeast organism. A skin test has not yet been made. An old lady of 79 has had ulcers on various parts of her body for eight months past.

Yeast cells were found in the pus from one of these ulcers and could easily be recognized both in unstained and stained specimens. The remaining three patients have a severe cough, and a prominent feature is the profuse fetid expectoration and the frequent attacks of "cold." We are hoping for something more definite from the study of these cases.

SUMMARY

A yeast which has been identified as a saccharomycete has been observed in the sputum of a number of patients with anomalous lung conditions, also in a tonsil membrane, a vaginal discharge and in pus from a skin abscess. It was mixed with other organisms in most cases, but has been found as the only apparent cause of infection in a few patients in whom disappearance of the organism has been followed by alleviation and disappearance of the symptoms.

Autobacterins made from this yeast organism have seemed to cause some improvement in three cases and an exacerbation of symptoms in one.

The most benefit has been derived from the use of the iodids in large doses. An extract prepared from this saccharomycete gave a slight reaction in a skin test on two patients. The serum of four patients gave a positive agglutination test for the yeast.

242 West Holt Avenue.

NOTE ON "A CASE OF PANCREATIC DIABETES
MELLITUS" BY HERMAN O. MOSENTHAL.*

GRAHAM LUSK

NEW YORK

This report by Dr. Mosenthal¹ contains a point which is not brought out in the description. If the table which gives the quantitative urinary analysis be examined, it will be found that, on those days in which protein and fat were given to the diabetic individual and carbohydrates rigidly excluded, the D:N ratios were respectively 3.75, 3.85 and 3.44. Thus on May 19, with a total excretion of 27.7 gm. of nitrogen, the D:N ratio was 3.75, and on May 24, with a total excretion of nitrogen of 11.8 gm., the D:N ratio was 3.85. It is also noticeable that the ammonia excretion remains comparatively low on these days, 2.9 gm. on one day and .9 gm. on the other day.

These conditions are very like those in the case reported by Mandel and Lusk.² At the time of their investigation, they termed the ratio 3.65 the fatal ratio, a condition in which combustion of carbohydrates is essentially impossible. Since clinicians in general have hesitated about withdrawing carbohydrate completely from the diet of diabetics, there are few cases on record in which the results of Mandel and Lusk have been confirmed. It appears, however, from this work of Dr. Mosenthal, that, if the ammonia excretion remains low — which, of itself, indicates that the acidosis is not high — then one may, during a short period at least, withdraw carbohydrate completely from the diet and determine the D:N ratio without injury to the patient.

1. THE ARCHIVES INT. MED., 1912, ix, 339.

2. Deutsch. Arch. f. klin. Med., 1904, lxxxi, 472. For further information consult Lusk, Jour. Am. Med. Assn., 1904, xliii, 241, and 1910, lv, 2105; THE ARCHIVES INT. MED., 1909, iii, 1; Science of Nutrition, 1909, p. 299.

PELLAGRA IN ILLINOIS

CONDENSED REPORT OF THE ILLINOIS PELLAGRA COMMISSION *

In this report the results of the various investigations which have been undertaken, together with those reported to this Commission by other observers, have been incorporated in one article. The material has been to some extent condensed and summarized in order to eliminate unnecessary details, which can be found by those interested in the detailed report made to the Governor of Illinois. This detailed report will be published shortly in the form of a monograph and copies sent to all important libraries in the United States.

At this point we wish to express our acknowledgments to those who have so materially helped in the compilation of this report by sending us personal communications. They include Captains J. F. Siler and H. G. Nichols of the United States Army, detailed by the courtesy of Surgeon-General Wyman, on the request of Governor Charles S. Deneen, to study pellagra in Illinois; Prof. Stephen A. Forbes, Entomologist to the State of Illinois; Dr. J. F. Waugh of Chicago; Dr. Arthur D. Hirschfelder of Baltimore, and Dr. Sidney D. Wilgus, Superintendent of the Kankakee State Hospital. We would also especially express our thanks for the unfailing courtesy and assistance of Dr. George A. Zeller, Superintendent of the Peoria State Hospital, without which we should have been sorely handicapped. We have also received much assistance from other sources, and would mention especially Dr. J. T. Rooks, Mr. A. F. Wussow, Mrs. Josephine (Kerr) Allison, Miss Mattie A. York, Dr. L. J. Pollock and Dr. C. E. Smith, who have performed a great deal of the detailed work on which this report is based.

I. CURRENT VIEWS ON PELLAGRA

There is no need in this report to enter extensively into the history and geographical distribution of pellagra, since many excellent treatises are available. The disease was apparently first described by the Spanish physician Casal in 1735, although this was not published until after his death in 1762. The following paragraph quoted from the monograph by the late Dr. J. N. Hyde of Chicago¹ will sufficiently indicate the wide distribution of the disease:

*Dr. Frank Billings, President.
Dr. J. L. Greene, Vice-President.
Dr. Oliver S. Ormsby, Secretary.
Dr. George W. Webster.

Dr. H. S. Grindley.
Dr. Howard T. Ricketts.
Dr. H. Douglas Singer.
Dr. W. J. McNeal.

1. Hyde, J. N.: Pellagra and Some of its Problems, *Am. Jour. Med. Sc.*, Jan. 7. 1910.

Frapoli, of Milan, in 1771, is commonly reported as first to have given the name to the disease by which to-day it is most generally known, but in fact he merely reproduced a title current among the people of his day: "*Morbus vulgo, Pellagra.*" In the long list of authors who followed, from Strambia, Marzari, Alibert, Rayer and Raymond, to Lombroso, Sandwith, Babes and Sion, and Sir Patrick Manson, can be traced the progress of the disease in Europe from Spain to southern France, northern and central Italy, Corfu, upper Egypt and other parts of Africa, Austria, Servia, Bulgaria, Roumania, Asia Minor, India, Mexico, Barbadoes, and portions of North and South America.

With regard to the etiology of pellagra numerous views have been promulgated and it is well to say that the members of this commission entered on this study without prejudice or preconceived ideas with regard to the nature of the disease or its causation. The plans on which the work has been organized have been aimed towards the consideration of all the manifold theories which have been evolved in order, if possible, to narrow the lines of research into some more or less definite channel. The great drawback of most of the work which has so far been carried out, is that the investigator has started with some hastily-formed hypothesis, based on coincidences or chance observations which have not been submitted to careful scientific analysis. He has then been only too willing to see and insist on the pellagrous nature of the most variable symptoms produced in lower animals as the result of experiments founded on such hypothesis.

One of the best critical reviews of previous work on pellagra will be found in the Progress Report of the British Commission for the Investigation of Pellagra, by Louis W. Sambon²; especially in regard to the relation with maize. Free use has been made of this article in compiling the following statements.

The various theories which have obtained may be subdivided under two main headings: (1) Those concerning maize or Indian corn; (2) those alleging other causative agents. The supporters of the first group are commonly known as zeists and of the second as antizeists.

1. Theories which allege some causative relation between maize and pellagra have been most widely accepted, but are gradually losing ground. They have been and still are almost universally believed in Italy where this disease is probably more prevalent than in any other part of the world. This is largely due to the influence of Lombroso, by whom it was firmly believed and widely expounded, with the result that the Italian government was led to promulgate laws dealing with the use and care of Indian corn. In fact Sambon with considerable justice points out that the Italians have been studying corn rather than pellagra.

Various authorities differ in their views as to the nature of the relationship between corn and pellagra. These views may be briefly classed under the following headings:

2. Jour. Tropical Med. and Hyg., 1910, pp. 271, 282, 305 and 319.

(a) According to Lussana, Frua and others, Indian corn is deficient in or lacks some nutrient principle necessary for health, and pellagra results from a diet consisting too exclusively of maize.

As a corollary to this view should also be mentioned other conditions of malnutrition. Pellagra is unquestionably a disease which occurs most frequently among the poorer and less well-fed classes, and some have regarded it as the direct result of insufficient food. In most of the different theories malnutrition and defective hygiene are given as contributory factors.

(b) Corn contains some toxic substance which, in individuals who are especially susceptible for any reason, gives rise directly to pellagra.

(c) Maize undergoes some form of decomposition, as the result of the growth of bacteria, in the intestine of certain individuals. The toxins resulting from this change give rise to pellagra.

As will be observed, these theories deal with maize which is healthy in itself. The following views concern maize which is damaged or spoiled in some way:

(d) That healthy maize is innocuous, but that at some stage in its preparation for consumption either in the ear, when stored or after being cooked, it undergoes decomposition as the result of the growth of certain fungi. Various molds and bacteria have been isolated and incriminated by different authors; e. g., *Penicillium glaucum* (the commonest variety of mold), different varieties of *Aspergillus*, *Sporisorium maydis*, *Ustilago maydis* (smut), *Bacterium maydis*, *Bacillus pellagræ*, etc. It is supposed that toxins are produced in this process of decomposition which, when absorbed, cause pellagra.

(e) That some one of these organisms, which are commonly found on molded or spoiled maize, and which may be eaten with it, directly invades the human body where it elaborates toxins causing pellagra.

2. The antizeist views regard the disease as a specific infection of the body with a parasitic organism either bacterial or protozoal in character.

(a) The causative agent is some bacterium of unknown nature and habitat. This view is obviously similar to that given under 1, (e), but differs in that it does not specify any relation to maize.

(b) An infection with some variety of ameba or other protozoon. The frequency of concomitant amebiasis in pellagra has been emphasized by many authors, notably Long in this country. Alessandrini, in Italy, claims to have found a filarial infection of certain wells in pellagrous districts.

(c) That the disease is due to a protozoal infection of the blood stream in much the same manner as malaria and trypanosomiasis (sleeping sickness). These views are all based on supposed resemblances in the

epidemiology, endemicity, seasonal occurrence, etc., to these diseases. Some authors have also urged in support of this view the results of treatment. Sambon, who is one of the chief exponents of this view, goes to the length of incriminating some species of *Simulium* (the black-fly, sand-fly or buffalo gnat) as being the agent which carries the organism and by biting the human host injects the protozoa into man. It should be stated that Sambon formulated this hypothesis even to the naming of the carrier as the result of comparative reasoning before entering on his investigations. The hypothesis is attractive and plausible in many respects, but so far lacks much more evidence that simulia are the carriers than the fact that in many places simulia and pellagra are found in the same locality.

This list does not exhaust all the theories which have been propounded, but it covers the grounds that have been considered in the work carried out by this Commission.

II. PELLAGRA IN ILLINOIS

Pellagra was first recognized in the State of Illinois at the Cook County institution at Dunning about June, 1909. The diagnosis, first made by Dr. L. J. Pollock, was reported to Dr. W. A. Evans, Health Officer of Chicago, and was confirmed at his request by Passed Asst. Surgeon C. H. Lavinder of the Public Health and Marine-Hospital Service in July. Shortly afterwards cases were recognized at the Peoria State Hospital and at the Elgin and Kankakee State hospitals. The diagnosis once made, the managing officers and medical staffs at Dunning and Peoria were able to recall instances of exactly similar eruptions in the past although it was of course impossible to gather any figures which could give any idea as to the actual number of cases. We have therefore thought it advisable to collect only those cases which have been definitely diagnosed since July, 1909. It has been also thought wise to exclude all cases in which there seemed to be any doubt as to diagnosis, although this will probably result in an underestimate of the actual numbers. Another fact which will also tend to render the figures smaller than they should be is that at present the disease is still but little known by the profession at large, and there are undoubtedly cases which are not recognized both inside and outside the state hospitals for the insane. Many attacks are probably of extremely mild character and are not accompanied by any, or but the most transient, constitutional symptoms and are consequently not called to the attention of medical men. It is possible also that errors in diagnosis may have the opposite effect of swelling the totals, as we have seen various skin diseases which have been diagnosed as pellagra, and until the medical profession becomes better acquainted with the characteristic features of the disease it will probably be impossible to get data which are absolutely reliable.

With regard to cases occurring outside the state and county hospitals for the insane, but little reliable information is available. We have been able to collect a few cases, mainly through the kind offices of Dr. George A. Zeller. The State Board of Health has apparently no information on the subject.

The figures for the number of cases in the different institutions, including those at the Cook County institutions at Dunning, have been furnished by the superintendents of each institution with the exception of Peoria, where they are the result of data furnished by Dr. Zeller and the hospital medical staff, by Captains Nichols and Siler and by personal observations at frequent intervals by the members of this Commission. During the height of the pellagra seasons all patients who have previously had attacks of the disease have been examined for evidences of recurrence and on several occasions all patients in the institution have been inspected. Visits have also been made to suspects and others at the Jacksonville, Anna, Watertown and Elgin state hospitals.

Table 1 presents the total number of cases occurring in the three periods, August, 1909, to January, 1910; January, 1910, to January, 1911, and January, 1911, to Sept. 1, 1911, in so far as we have been able to collect them. Recurrent attacks in individuals recorded as pellagrins for the preceding periods are not included a second time, so that the figures represent the actual number of persons attacked.

TABLE 1.—TOTAL NUMBER OF CASES OF PELLAGRA OCCURRING IN ILLINOIS INSTITUTIONS 1909, 1910 AND 1911

	1909		1910		1911		Total			Dead†	Case Mor-tality
	M	F	M	F	M	F	M	F	Total		
Anna S. H.	3	0	3	0	6	0	6	2	33.3
Elgin S. H.	3	7	2	2	20	4	25	13	38	12	31.6
Jacksonville S. H. ..	0	0	1	0	0	0	1	0	1	0	0.0
Kankakee S. H.	0	5	0	2	*1	*4	1	11	12	5	41.7
Peoria S. H.	73	104	*42	*25	5	9	120	138	258	128	49.6
Watertown S. H.	0	0	0	*1	0	2	0	3	3	3	100.0
Chester S. H.	0	0	0	0	0	0	0	0	0	0
Lincoln S. S. & C.	0	0	0	0	0	0	0	0	0	0
Dunning C. I.††	14	14	18	17	6	7	38	38	76	30	39.5
Cook County Hospital	1	2	5	0	6	2	8	6	75.0
Elsewhere	1	1	2	2	3	3	6	3	50.0
Totals	'90	130	68	50	42	28	200	208	408	189	46.3

*One was admitted to the hospital with the disease fully developed. See Table 2.

†With the exception of those for Dunning the numbers given in this column include all deaths in pellagrins whether immediately due to pellagra or not.

††The figures furnished to the Commission for each year were totals only. It was, however, stated that the sexes were equally affected and hence the figures given for each sex have been estimated by dividing the total by two.

It should be stated that at most of the institutions there have been patients not included in the figures in this table, presenting some suspicious appearances not sufficiently definite in character to justify a positive diagnosis. At Peoria, in 1909, there were a number of such cases and we have a list of forty-nine suspects in 1910. It is probable that some of them were pellagrous, whereas others certainly were not.

In Table 2 is given a list of the cases outside the hospitals for the insane concerning which we have been able to obtain definite information. Dr. Ormsby has kept careful watch on suspected cases at the Cook County Hospital and the diagnosis has been confirmed by him in all those instances recorded in the table. For the sake of completeness there has also been added to this table a list of the cases which have been admitted to the hospitals for the insane with the disease already developed.

TABLE 2.—PELLAGRA CASES OCCURRING OUTSIDE THE HOSPITALS FOR THE INSANE

Age	Occupation	Sex	County	Town	Urban or Rural	Hospital	Physician	Result
30	Housewife	F	Cook	Chicago	C	Cook County	S. Kuh	F
58	Switchman	M	Cook	Chicago	C	Cook County	O. S. Ormsby	F
44	Porter	M	Cook	Chicago	C	Cook County	O. S. Ormsby	F
47	Laborer	M	Cook	Chicago	C	Cook County	W. A. Pusey	F
40	R. R. Agent	M	Cook	Chicago	C	Cook County	O. S. Ormsby	R
43	Housework	F	Cook	Chicago	C	Cook County	W. A. Pusey	F
50	Liveryman	M	Cook	Chicago	C	Cook County	O. S. Ormsby	F
42	Upholsterer	M	Cook	Chicago	C	Cook County	S. R. Slaymaker	R
37	Housewife	F	Peoria	Peoria	C	J. H. Bacon	F
40	Laborer	M	Peoria	Peoria	C	J. H. Bacon	R
60	M	Peoria	Peoria	C	Dispensary	J. H. Bacon	R
38	Rag picker	F	Peoria	Peoria	C	St. Francis	R. L. Green	R
46	Housewife	F	Knox	Galesburg	C	J. H. Bryant	F
61	M	Vermilion	Danville		C. E. Wilkinson	F

Cases admitted to the State Hospitals with the eruption present.

91	None	M	Henderson	Poor farm		Peoria S. H.	R
54	None	M	Woodford	Washburn	R	Peoria S. H.	F
42	Baker	F	Mason	Havana	R	Peoria S. H.	F
57	Housework	F	Grundy	Mazon	R	Kankakee S. H.	F
63	R. R. Foreman	M	Cook	Chicago	C	Kankakee S. H.	R
..	F	Carroll		Watertown S. H.	F

City; R, Rural or small town; F, Fatal; R, Recovered from this attack.
Case 6 is recorded in detail in the section on clinical and pathological studies. (Case 1, A. D. p. 159.)
lived in Mississippi but no attacks had been observed while there.
Cases 9 and 10 were sister and brother. Case 9 had seven attacks in seven consecutive years.
Case 11 had an attack also in 1910 as well as in 1911.
Case 13 had removed to Galesburg from Peoria three months before the onset of symptoms and possibly to the Peoria group of cases, although no previous attack was known.
Case 14 lived in West Lebanon, Ind., and went to Danville for medical treatment. He had attacks 1909, 1910 and 1911.
Case D. S., recorded in detail, in full report.
Case J. V., recorded in detail, p. 162.
This man had had previous attacks in the Panama Canal Zone.

It should further be mentioned that we have heard rumors of cases in Canton, Fulton County, and also in Henderson, Williamson and Rock Island counties.

The statistics relating to the Peoria State Hospital will be found in Tables 3, 4, 5 and 6. The first of these shows the average age, the number of cases arising in each decade of life and the relative numbers affected of the two sexes. In Chart 1 is shown a curve representing the month in which attacks have started. The date of onset has often been difficult to fix as it may be extremely insidious and accompanied by but few or no constitutional symptoms. The patients furthermore do not complain of

TABLE 3.—ANALYSIS AS TO AGE, ETC.

	Average Age*	Decade of Life								Sex		Total
		2nd	3rd	4th	5th	6th	7th	8th	9th	Males	Females	
1909	52.3	7	27	40	44	42	14	3	0	73	104	177
1910	57.1	1	9	10	15	20	7	3	2	42	25	67
1911	55.1	0	1	3	5	3	2	0	0	5	9	14
Total	53.7	8	37	53	64	65	23	6	2	120	138	258

*Youngest 22; oldest 93. Males are to females in the proportion 1:1.15.

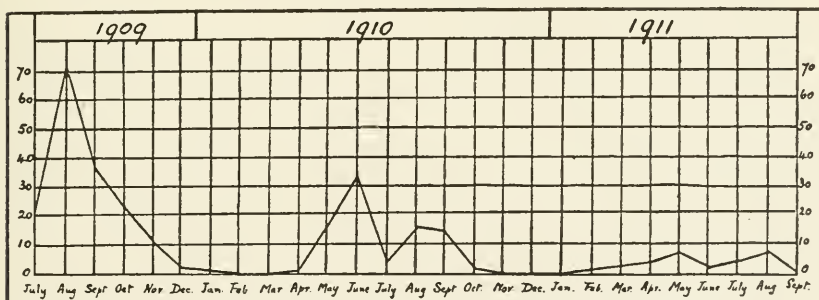


Chart 1.—Curve representing the months in which the attacks started.

the eruption and often belittle its importance when it is called to their attention. In many cases they are so inaccessible as the result of dementia that direct examination is necessary in order to discover any evidence at all. The figures given in Chart 1 therefore cannot be regarded as entirely accurate, but represent approximately the months in which the disease appears to have become acute. The onset of recurrent attacks has been included in the figures given. It will be observed that one case was noted in January, 1910, and another in February, 1911. Both of these were recurrences in individuals who had had attacks in the preceding year.

In Table 4 are recorded the number of recurrences in patients who have had known previous attacks. Occasionally it is found that patients in whom a positive diagnosis is made are said to have had attacks in previous years, but these have in each instance been recorded as new cases. One of those given as a new case for 1911 is said to have had an attack in the summer of 1910. Furthermore, four of the patients who unquestionably had pellagra in 1909, showed two exacerbations in 1910 which have been recorded, in order to avoid confusion, as only one recurrence for each during that year.

TABLE 4.—TABLE OF RECURRENCES

	New Cases	Deaths July, 1909, to May, 1, 1910	Living in Pellagra Season of 1910	Recurrences in 1910	Percentage of Re- currences in 1910	Deaths May 1, 1910, to May 1, 1911	Living in Pellagra Season of 1911	Recurrences in 1911	Percentage of Re- currences in 1911	Deaths May 1, 1911, to Sept. 1, 1911	Living on Sept. 1, 1911
1909 ..	177	97	80	25	31.25	12	68	9	13.24	1	67*
1910 ..	67	11	56	5	8.9	3	53†
1911 ..	14	4	10‡
Total ..	258	124	14	11.3	..	130

*Five of these are now at Kankakee.

†Three of these have since died.

‡Two of these have since died.

In Table 5 is shown the mortality at the Peoria State Hospital. It will be noticed that in a very large percentage death is recorded as being directly due to pellagra. This must certainly be questioned for the year 1909, because at that time there was also an epidemic of amebic dysentery, many of the autopsies showing amebic ulceration of the intestine, in the walls of some of which the amebæ were demonstrated by Captains Nichols and Siler. Two cases of liver abscess of typical character were also seen. It has seemed impossible in many cases to determine what weight is to be assigned to pellagra as the primary cause of death and how much belongs to any other coexisting disease. It has therefore seemed advisable to make no subdivision which could only be misleading. In those cases recorded as dying from some other cause there were no active pellagrous symptoms present at the time of, or shortly before, death.

In discussing these tables attention may first be directed to the class of individuals most affected. In general it may be said that the disease is especially frequent for some reason, at present unknown, among the chronic insane. Most of the patients who have suffered from pellagra have belonged to the groups of defectives, senile dementes, epileptics and

the terminal stages of dementia præcox. They have been for the most part poorly nourished and in an enfeebled state of bodily health. The total population of the Peoria State Hospital during the great epidemic of 1909 was about 2,100, and of this number of patients we find at least 8.4 per cent. showed definite symptoms of pellagra. Yet during this period none of the employees suffered from the disease in spite of the fact that they were exposed fully as much to the bites of insects and drew their food and water supply from exactly the same source as the patients. This freedom from pellagra on the part of physicians, nurses, attendants and other employees has been absolute in all the institutions. It is, furthermore, almost certain that some of these employees have been in a run-down state of health at some time during the seasons in which pellagra was rampant.

TABLE 5.—MORTALITY AT THE PEORIA STATE HOSPITAL

	Pellagra Given as Immediate Cause		Other Causes		Total Deaths	Percentage of Cases
	Number	Per cent.	Number	Per cent.		
1909	89	81.0	21	19.0	110	62.15
1910	8	63.7	6	36.3	14	16.42
1911	4	100.0	0	0.0	4	28.57
Total	101	78.9	27	21.1	128	49.61

OTHER CAUSES OF DEATH

Pulmonary tuberculosis	6
Valvular heart disease	4
Pneumonia	4
Epilepsy	2
Cerebral hemorrhage	2
Cerebral embolism	1
Cholecystitis	2
Amebic dysentery	1
Chronic nephritis	1
Senile gangrene	1
General paralysis of the insane	1
Carcinoma uteri	1
Accidental	1

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While the general statement made above is true that the individuals have been weakly and ill-nourished, there are, however, notable exceptions. Some of the pellagrins have been apparently robust and well nourished. In this connection it may be of interest to refer to a patient seen by Dr. Oliver S. Ormsby in 1911, who does not figure in the tables given here, as the disease was contracted in Kentucky and the patient came to Chicago only for medical advice. This lady was 44 years of age, native of Maine, but had lived in Kentucky for twelve years, where she was at

the head of a college department of domestic science. Her duties, therefore, consisted of the teaching of hygiene as regards management and dietary of the household. She had had attacks of "morning diarrhea" for several summers and was subject to attacks of acute indigestion. The first known attack of dermatitis occurred in October, 1910, but was very mild and without severe constitutional symptoms. The second attack, in 1911, was much more severe and led her to come to Chicago for assistance. When seen she presented an entirely characteristic skin eruption of pellagra involving the hands, arms, forearms and across the sternum, with sore mouth and diarrhea. In spite of this she appeared to be in a good state of nutrition. With such facts before us it is certainly difficult to understand the freedom of hospital employees.

Attention should be directed to the coexistence of intestinal parasitism with the larger outbreaks of pellagra at the Peoria State Hospital; 1909 also saw an epidemic of amebic dysentery and we find that since that year pellagra has subsided very rapidly. It is of course possible that the enormous fatality during 1909 may have removed most of the more susceptible individuals. The question of the relation of protozoal infection to pellagra is more fully discussed in later sections of this report.

The dietary of the state hospitals is also the subject of detailed study later. It may, however, be mentioned here that the most notable point in the dietaries has been a deficiency of animal protein, and yet the institution feeding the smallest amount of meat, which forms the main source of this material, has shown no pellagra.

A few words are available in regard to the habits of the patients which would expose them to biting by insects, etc. In all institutions patients are out of doors as much as possible. At Peoria probably the majority of the patients who have contracted pellagra have spent the time, while out of doors, sitting on the porches of the buildings which they leave only for a short time if at all. So many have been more or less helpless demented that any more active outdoor life has been out of the question. Others it is true have had the free run of the grounds. It should be noted that this outdoor period of the day does not include the early morning and late evening, at which time blood-sucking insects would be most prevalent. Furthermore, many attacks of pellagra have arisen in patients confined to the hospital wards, who were not out of doors at all.

In this connection reference may be made to the striking example quoted by Dr. Hyde¹ from the Elgin State Hospital. The patient, a woman, had been bedridden for years and occupied a room in common with another insane woman, also pellagrous. The first patient occupied a bed at the farther extreme corner of an apartment lighted by a single window. The only light accessible for a long period prior to the advent

of the pellagrous disorder was furnished by this one window. It is but fair to state that inquiries at the Elgin State Hospital failed to elicit the name of this patient, but the medical staff has changed since this observation was made (1909). The facts are substantiated, however, by Dr. Ormsby, who was with Dr. Hyde on the occasion of the visit.

With regard to insects such as fleas, bed-bugs and body-lice, it cannot be said that any institution is entirely free from them, but they certainly are not numerous in any of the hospitals where constant warfare is maintained against them.

The distribution of the cases in the different wards and buildings at the Peoria State Hospital, built strictly on the cottage plan, revealed no special foci. Cases apparently originated in all of them and were not more common even in those cottages in which a large number were segregated for observation. Furthermore, there were no differences in the dietary of the different wards with the exception of the hospital wards, all being supplied from the same kitchen.

DISTRIBUTION

As regards the distribution of pellagra throughout the state outside the hospitals for the insane, we feel that the data are still too few to justify any conclusions. It is certainly striking that the great majority of the cases on which we have definite information have arisen in persons living and working in the two largest cities in the state, Chicago and Peoria. This is contrary to general experience in Italy and elsewhere. Sambon states that pellagra does not occur in big cities and bases much of his reasoning as to the relation with simulia on this point. He claims that simulia do not enter large cities or human habitations. In this respect he is certainly wrong as regards some species, e. g., *S. venustum*. Sambon believes the disease to be almost confined to agricultural laborers and explains the few instances in which city dwellers have been affected by occasional visits to the country. Such reasoning is difficult to refute as most people occasionally go beyond the city limits. There seems to be one possible explanation for the difference in the experience in this state as compared with that in Italy. The disease has only recently been recognized here and it is obvious that the country practitioner is likely to be the last to become informed concerning it. Nevertheless there has been so much written in the lay, as well as the medical, press concerning the disease that it seems hardly possible that the majority of the doctors throughout the country districts have not become acquainted with its prevalence and very striking and obvious characteristics. A further fact is also pertinent on this point. If, as is claimed by those most competent to judge, pellagra leads sooner or later to manifestations of mental disorder, surely the state hospitals would be receiving more examples.

Judging from the experience of Sambon in Italy, if the disease were so much more common in agricultural communities than in large cities, there should be several hundred pellagrins in the country districts to balance the few we have been able to collect in Chicago and Peoria among persons who are strictly city dwellers. This point can only be determined by a careful investigation of the rural population of the state, and seems to us a very proper subject for investigation by the State Board of Health.

Until such investigations are made it would be unwise to attempt to state the probable number of pellagrins at present in the state of Illinois. Our tables show that there has been a marked decrease in the number of fresh cases at the Peoria State Hospital, whereas at Elgin they have increased. But another fact which must be regarded as disquieting is that the numbers outside the state hospitals, while still very small, are increasing. It seems to us advisable that every effort should be made to determine the actual numbers at the earliest possible date in order to be able adequately to determine the progress which the disease is making. As a conservative estimate we would say that since July, 1909, when the disease was first recognized, there have been 500 cases in this state.

III. CLINICAL AND PATHOLOGICAL

It has not been thought necessary to include in this report a detailed description of the various manifestations of pellagra, since many excellent articles covering this ground have already been published by various authors.¹ We propose to give only the results of our own observations, with brief descriptions of the main characteristics. With regard to pathological material, we have been at a disadvantage in that it has been difficult to obtain necropsies on undoubted cases until within the past few months. The microscopical examination of the nervous system is consequently yet far from complete. The cases on which the pathological examinations were made are reported in some detail below and have been obtained from the following sources:

Case 1 was studied by the courtesy of Dr. W. A. Pusey at the Cook County Hospital; Case 2 from the Kankakee State Hospital; Cases 3, 4, 5 and 6 from the Elgin State Hospital; the autopsies with the exception of three being performed by the medical officers of that institution; Cases 7 and 8 were from the Peoria State Hospital, the autopsy in Case 7 having been performed by Dr. Ellis of that institution.

The clinical study has been made on six cases transferred from the Peoria to the Kankakee State Hospital, on cases arising in the latter hospital, together with material collected on frequent visits to Peoria.

Cutaneous System.—In a study of more than two hundred patients, the manifestations exhibited on the skin were sufficiently characteristic

to enable one to make a diagnosis of the general condition. In general, the symptoms corresponded to the cases described abroad, in Italy and other countries. It can hardly be said, however, that they were exhibited in the stages which have artificially been made in European cases. Rather than being stages of disorder they appeared to exhibit degrees of activity of the process. The arrangement of the lesions was characteristic.

In the major portion of the cases the dorsum of the hands, the wrists, and some parts of the face, neck or scalp were involved. The disease only occasionally involved the feet or ankles, areas which were so often affected in the European cases. In a large number, the lesions occurred on the arms and chest; in a smaller percentage, the ears and other parts of the body were involved. In a very few, the inflammatory process involved the palmar surface of the hands, and occasionally the eruption was generalized. The peculiar collar described abroad, while seen here occasionally, was not common. In the case of several women, quite a severe dermatitis occurred about the vulva and involved the mucous membrane of the vagina. The lesions were always symmetrically placed and ran through a pretty typical course. In the major portion, the distribution on the hands was as follows: a solid area extending over practically the entire dorsal surface of the hand, involving the fingers to the knuckles, also the wrist on the extensor surface for a distance of about two inches. In the latter area it would frequently sweep around and involve about two-thirds of the flexor surface, then come to an abrupt ending. This particular gauntlet was interesting and occurred frequently.

In the most moderate degree of erythema, the process went through about the following course: Large macular lesions, light or dark red, would appear, which soon fused, forming a patch of dermatitis almost identical in appearance with that caused by the sun. After a period of from seven to fourteen days or a little longer, desquamation would begin, at which time a roughened scaling surface was presented. Early in the process, moderate to marked swelling was usually present. No subjective sensations were complained of. That none was present was manifest by the absence of any signs of interference on the part of the patient. In some patients, pigmentation occurred, while in others, after desquamation was complete, the area was lighter than formerly. In the more active cases, on the erythematous base bullous lesions would soon develop. Some of these were very large. After several days they would gradually dry, leaving a thickened, crusted epidermis. Secondary pyogenic infection not infrequently followed in the vesicular and bullous cases. In many, the edema was sufficient to produce fissures to quite a marked extent. The lesions, whether erythematous or bullous, were

always well defined. It was particularly noticeable that after the bullous lesions had cleared the skin was somewhat thinner than formerly and there was no hyperpigmentation. In the older patients, where the process was subacute, the areas presented the appearance of a simple chronic dermatitis with marked hyperpigmentation. The atrophy described in chronic cases in Europe was present to a slight degree only. Loss of pigmentation did occur, but true cutaneous atrophy has been uncommon. That sunlight played a part in producing or determining the location of lesions was demonstrated by having suspected patients wear fenestrated gloves, when the eruption would be largely limited to the exposed surfaces. We have, however, seen many patients exhibiting typical lesions occupying the hands and other usual areas who were not exposed to the direct rays of the sun at any time. Bedridden patients developed lesions in the same situation as those able to be out of doors. That the cutaneous lesions resemble an ordinary sunburn was frequently emphasized by reports of attendants stating that certain patients were suffering from sunburn, which on examination proved to be a pellagrous erythema. The importance of the cutaneous symptoms is at present paramount, for without them a diagnosis can rarely be made. It is probably true that the disease may occur without these symptoms, but in the present state of knowledge they are essential in arriving at correct conclusions.

Pathology.—Cutaneous: In a large number of sections studied, the general picture was that of an angio-neurotic process, and resembled to a marked extent that seen in multiform erythema. The most marked change was noticed in the superficial part of the corium, almost all infiltration occurring in the pars papillaris. The specific findings are as follows: With a low power, the stratum corneum was thickened, the stratum granulosum and rete practically normal. The upper portion of the corium showed inflammatory reaction, and the connective tissue appeared edematous. With a high power the hyperkeratosis was seen to be well marked. Here and there, areas of parakeratosis were present, as evidenced by the presence of nuclei extending to the upper layer of the stratum corneum. Many pigment granules were present. The rete was practically normal, except in places where its integrity was interfered with by infiltrating cells. In the papillary layer cellular infiltration was quite marked, particularly in the region of blood vessels. Collagen and elastin were present, the former showing edematous changes. The deeper parts of the corium were comparatively normal. In parts of the papillary layer elastin was absent.

From a survey of these findings, no specific statement can be made concerning the process. No microorganisms were found. That the process was moderately destructive, was evidenced by the absence of certain structures. As a whole, there appeared to be a reaction on the

part of the skin either to a local toxic irritant or an angio-neurotic process influenced from a distant focus.

Gastro-Intestinal System.—The symptoms referable to this system unquestionably stand next in importance to the skin lesions and are present in a very large proportion of all cases. They seem to be especially marked in all more severe examples. They cannot, however, be regarded as characteristic inasmuch as very similar manifestations are also met with in other disorders. We would hesitate to base a diagnosis upon them in the absence of typical skin lesions.

The tongue becomes swelled and denuded, presenting a bright red appearance with, in severe cases, more or less ulceration along its edges and on its under surface and the appearance of yellowish sloughs in these regions which bleed very easily. The lips and cheeks, where they come in contact with the teeth, also show, in the more serious forms, a similar bleeding, sloughy appearance. The whole condition presents features which are very similar to the aphthous stomatitis seen in other debilitating states, especially in children, but also in adults, as, for example, in pemphigus. The ulcers are always superficial and in the event of recovery heal without leaving scars. This state of the mouth is often very painful and renders eating difficult. In the slighter forms there is usually nothing more to be seen than a redness and smoothness of areas, especially at the tip and along the margins which has received from Sandwith the name of "bald-tongue." Scrapings from the sloughing surface have not shown the presence of any mycelial growth.

Diarrhea has also been a very constant concomitant, being as a rule more severe in those cases which terminate fatally. In the milder cases close questioning may be necessary to find that there has been a looseness and excessive action of the bowels and we have in some been able to obtain no such evidence. In this regard some attention must be paid to the class of patient with whom, in the main, we have had to deal, a class of chronic dementals from whom but little information can be obtained directly. Nevertheless, it has appeared that in some there has been either no change in the usual state of the bowels, or there has been even constipation. The appetite may be preserved and in some cases it has even appeared to be excessive, especially in relation to the actual digestive capacity. In more severe cases, however, appetite is poor.

Mental and Nervous System.—The classical descriptions of pellagra give somewhat vague accounts of the symptoms due to involvement of the nervous system, especially in regard to the mental picture. The material at our disposal is unfortunately almost entirely unsuited for a study of this question, since almost all cases have arisen in patients already suffering from mental disorder and presenting more or less evidence of interference with the projection system. In most instances

the records of previous examination of the nervous system are almost entirely lacking and it is hence impossible to decide which, if any, of the present manifestations are due to pellagra. In Cases 1 and 2 recorded below, and another seen with Dr. Baker of Peoria, where pellagra occurred in individuals previously healthy, there were no evidences of gross lesion of the nervous system except in the final stages. The exaggeration of reflex did not appear to be more than could be accounted for by the condition of exhaustion. In the final stages there have in many cases developed symptoms of central neuritis, and this must unquestionably be regarded as worthy of more than passing mention. It will be discussed further in considering the course of the disease.

With regard to mental symptoms, we can quote but two cases which bear on the point. In the first of these there developed a psychosis of delirious character which appeared to run parallel to the physical manifestations. Besides this, there was an intensification of the querulousness peculiar to the personality of the patient together with some depression and irritability. In the second case a typical manic-depressive excitement arose shortly after the appearance of gastro-intestinal symptoms which seems to have been the early manifestations of an attack of pellagra. The scanty history of this individual prior to the onset which was available, seemed to indicate that she had had periods of depression with mutism and apathy, which would suggest the occurrence of transient depressed phases of manic-depressive insanity. Hence one is not justified in regarding the manic excitement as a picture forming part of the pellagra complex. It is to be considered only as a personal type of reaction.

In Case 1, quoted below, the patient showed no mental symptoms up to the time of her death beyond a change in disposition in which she became more depressed and irritable. This may be considered as probably adequate to her general condition of weakness and exhaustion. Another case of interest in this connection is that seen by the courtesy of Dr. J. H. Bacon² in the city of Peoria. In a personal communication Dr. Baker informs us that this patient, who had seven attacks of pellagra in seven consecutive years, had become more irritable and depressed ever since the first attack in 1903, but there were no more definite mental symptoms until the last and fatal attack in 1910. The depression then became more marked although still accompanied by insight. During the last stages she also had episodic periods of apprehensive excitement accompanied by sense falsifications and extreme restlessness. These episodes occurred mostly at night and were followed by amnesia. During them she threatened suicide, accused her daughter of immorality and

2. Bacon, J. H.: A Case of Pellagra in Illinois. Jour. Am. Med. Assn., May 28, 1910, p. 1783.

heard robbers trying to break into the house. During the intervals she was depressed and hopeless but was able largely to direct the affairs of her household from her bed.

Among individuals already insane there have been no definite changes produced by the onset of pellagra. Some are reported as having been more restless and excited, others have seemed more depressed and irritable but in the vast majority the pellagra does not seem to have led to any change in the mental attitude of the patient.

From our personal experience we therefore do not feel justified in making any very definite statements regarding the nervous and mental symptoms of pellagra. It has seemed that in the projection system there are no characteristic changes until the final stages when there is a great liability to the occurrence of central neuritis. (In this relation the observation of increased sensitiveness of nerve trunks and muscles to pressure, made in Case 2 at the time of a generalized pellagrous eruption, is of considerable interest in that it suggests that the nerve trunks are susceptible to the pellagrous toxin whatever be its nature.) In regard to the associative system of the brain, our observations would suggest that there is a liability to the occurrence of deliria similar to those seen in other infective and toxic states. Here reference may be made to the report of the Georgia State Sanitarium at Milledgeville for 1910. A large number of patients were admitted to this institution suffering from pellagra with mental symptoms and it is interesting to note that the psychoses presented are included in the infective-exhaustive group which contains the deliria due to bacterial and other organic toxins. Apart from this acute condition, which is to be regarded only as a type of reaction on the part of the brain to acute intoxication of any kind, there does not seem, in our limited experience, to be any "pellagrous insanity." The change in disposition, which is not by any means constant, is very similar to that seen in other chronic exhausting diseases such as *tubes dorsalis* and tuberculosis.

In our opinion it still remains to be proved that pellagra gives rise to any more chronic form of nervous or mental disorder. It does give rise to symptoms of acute intoxication of the nervous system, such symptoms being not in any way characteristic of any particular toxin. Furthermore, like other intoxications, it may act as the exciting cause for the outbreak of acute psychoses, such for instance as those belonging to the manic-depressive group, in individuals who are susceptible.

There is one further point which is also especially worthy of emphasis, although its explanation is still to be found. This is the great susceptibility of the chronic insane to pellagra. The proportion of those affected outside the state and county hospitals for the insane to the inmates of these institutions is certainly extremely small in this state even if allowance be made for many failures to recognize the disease.

INTESTINAL BACTERIA AND PROTOZOA

1. *Bacteria*.—A very extensive study of the intestinal bacteria has been carried out, the results of which will be merely summarized here.

Altogether twenty-two stools from fourteen patients were examined as well as two samples taken from the intestinal canal post mortem in one of these fourteen cases. Of the first ten specimens, three, Nos. 5, 8 and 7, were furnished by inmates of the Kankakee State Hospital who showed a suspicious pigmentation of the skin, but in all probability did not have pellagra; five, Nos. 2, 3, 4, 6 and 9, were from pellagrins well on the road to recovery from an attack of the disease, which has not recurred in them up to the present time, August, 1911; two specimens, Nos. 1 and 10, were from pellagrins who had recently suffered a very severe acute attack and in whom the skin lesions had practically disappeared, although the patients still remained very weak and apparently about to die. The other fourteen specimens seemed to be, as a whole, more nearly representative of the condition of the stools in pellagra. Six of them, Nos. 11, 12, 14, 16, 18 and 20, were obtained at intervals from the same patient, W. N., and during this time the skin lesions evolved in such a way as to indicate an acute exacerbation of the disease, and the erythema appeared on a new area, the forehead, gradually extending downward over it; and finally, before the last specimen was obtained, the patient had recovered. Two specimens, Nos. 15 and 21, were obtained from another patient, the first one during a recurrence of the skin eruption, and the second after all skin manifestations had disappeared. One specimen, No. 13, was obtained from a patient in whom the skin lesion had persisted for months, indicating a chronic type of the disease. Two others, Nos. 17 and 19, were obtained from patients soon after the recognition of a recurrence of the skin eruption. Finally, the last three specimens were obtained from a fatal case in which the eruption had been present for three months, and was very severe at the time. One specimen, No. 22, was a fluid stool obtained forty-one hours before the death of the patient, and the second, No. 23, was obtained from the cecum, and the third, No. 24, from the ileum, at the autopsy, twenty-one hours after the death of the patient.

In the complete report, the observations have been recorded in detail. These included the numerical and differential counts of the bacterial cells in the feces; quantitative plate cultures of the mixed fecal flora on aerobic litmus-lactose-agar, aerobic litmus-lactose-gelatin, aerobic blood-agar, anaerobic litmus-glucose-agar and anaerobic blood-agar; Veillon-tube separation cultures in glucose-agar; plate cultures of the bacterial spores of the feces on aerobic litmus-lactose-agar, anaerobic glucose-agar and anaerobic blood-agar; fermentation-tube cultures of the mixed fecal flora in dextrose-broth, levulose-broth, lactose-broth and

saccharose-broth; plate and tube separation cultures from the sediments of these fermentation tubes; Gram-stains of these sediments; fermentation-tube cultures in litmus milk, in sugar-blood-broth and in broth containing coagulated egg-white; and finally, a study of certain bacterial strains isolated, including agglutination tests with the sera of pellagrins and others, and a brief study of the biological properties of a few of the bacterial strains. The agglutination tests, although they lead to no definite conclusions, are, perhaps, of sufficient general interest to warrant a brief summary here.

Of the 114 bacterial strains isolated from the different stools, fourteen were lost before being tested. These were the strains designated by the following numbers: 7, 15, 24, 31, 39, 40, 41, 42, 43, 45, 50, 61, 74 and 77. Each of the remaining 100 bacterial strains was subjected to one or more agglutination tests in which the serum of normal persons as well as serum from pellagrins was employed.

Cultures grown on inclined agar for 24 hours at 37 C., were employed for the tests. The anaerobic forms were incubated in an atmosphere of hydrogen. The growth was suspended in 0.8 per cent. salt solution and the heavier particles allowed to settle out. The supernatant suspension was diluted with salt solution until it was translucent, corresponding approximately to an empirical standard of density. The bacterial suspension was then mixed with an equal volume of a dilution of the serum in a small tube about 4 mm. in diameter. Several bacterial strains and several sera were always employed in each test, and among these there were usually at least one control bacterial strain and one control serum, the behavior of which had been previously ascertained. The tubes containing the mixtures of bacterial suspension and diluted serum were set up in a rack in parallel rows, each rank being made up of tubes containing precisely the same serum, and each file being made up of tubes containing the same bacterial suspension. The tubes were placed at 37 C. and observed at frequent intervals for twenty-four hours or longer. In the earlier tests, higher dilutions of serum (1:50) were employed. December 8 a test was performed with suspension of *B. typhosus* in different dilutions and with different dilutions of serum from a guinea-pig immunized to *B. typhosus*. As a result of this test, it was decided to employ a bacterial suspension of moderate density and to use the serum in a dilution of 1:10 for the preliminary tests of the various strains. The sera employed were derived (a) from healthy people; (b) from pellagrins, some in the active stage of the eruption and others without any existing manifestations of the disease; (c) from inmates of the state hospitals for the insane who had showed no signs of pellagra; (d) from sane individuals suffering from other diseases, such as typhoid fever, pneumonia and syphilis; and (e) from experimental animals.

Among these 100 strains only a few manifested any distinctly different behavior toward the sera of pellagrins as compared with the sera of normal individuals. These were Strains 14, 35, 44, 62 and 67, and possibly 85 and 88.

Following is a brief description of the characteristics of the five strains, 14, 35, 44, 62 and 67.

Strain 14 was derived from a thin colony, spreading beneath the surface, on an aerobic blood-agar plate inoculated with unheated suspension of Specimen 11. This specimen was a watery stool passed by the patient W. N. early in an exacerbation of definite pellagra. The culture was found to be impure and was separated into two strains by plating during January, 1911. The strain then designated as 14B gave the more definite agglutination reactions and was accepted as the authentic Strain 14, the other component being disregarded. The organism was an actively motile bacillus, varying in thickness from 1.0 micron to 1.8 microns and in length from 2.1 microns to 8.1 microns. The ends were rounded. In gelatin stab culture it produced a funnel-shaped liquefaction. In litmus-milk the reaction remained alkaline: the milk was slightly curdled after four days and the curd dissolved to some extent afterward. No gas was produced in broth containing dextrose, levulose, lactose, maltose or saccharose. There was no production of indol in Dunham's peptone-salt solution. On agar slants the growth was white at first but later became orange in color.

The contaminating organism separated from the above strain by plating the original Strain 14, was designated as Strain 14A. In its various characters it agreed closely with *B. coli*.

Strain 35 was derived from a colony on the aerobic blood-agar plates inoculated with unheated suspension of Specimen 14. This stool was passed by a pellagrin showing active erythema on the hands, but the usual precautions against the contamination of the stool were not carried out. The organism was an actively motile bacillus of about the same size as *B. coli*. In gelatin stab culture it produced a funnel-shaped liquefaction. In litmus-milk the reaction remained alkaline but there was slight coagulation after four days. No gas was produced in broth containing dextrose, levulose, lactose, maltose or saccharose, and indol was not produced in Dunham's peptone-salt solution. Pigment was not observed in the culture of this strain, so that it differed from Strain 14 in this respect.

Strain 44 was derived from a colony on the aerobic plates of litmus-lactose-agar inoculated with unheated suspension of Specimen 17. This stool was passed by a pellagrin showing a subacute, active erythema on the hands. The organism was an actively motile bacillus resembling *B. coli* in size and shape. In gelatin stab culture there was no lique-

faction, but gas bubbles were seen in the gelatin after three days. Litmus-milk was rendered acid in twenty-four hours and coagulated in forty-eight hours. No subsequent digestion of the clot was observed. Gas was produced in fermentation-tube cultures in broth containing various sugars as follows: Dextrose, 95 per cent. gas in the closed arm; levulose, 45 per cent.; lactose, 40 per cent.; maltose, 62 per cent.; saccharose, none. Cultures in Dunham's peptone-salt solution gave a pronounced positive reaction to the test for indol. Pigment was not observed in the cultures of this strain.

Strain 62 was derived from a colony on the anaerobic plates of glucose-agar inoculated with unheated suspension of Specimen 19. This stool was passed by a pellagrin with definite active pellagrous erythema on the hands, which had been noted first about three weeks before. The organism was a granular bacillus appearing somewhat larger than *B. coli*, some of the rods being very long. Most of the colonies on the set of glucose-agar plates were composed of similar bacilli. In gelatin stab culture there was no liquefaction, and gas bubbles were observed after eleven days. Litmus-milk was acidified in twenty-four hours and coagulated in forty-eight hours. There was no subsequent digestion of the casein. In fermentation-tube cultures in broth containing various sugars, gas was produced as follows: Dextrose, 45 per cent.; levulose, 45 per cent.; lactose, 45 per cent.; maltose, 50 per cent.; saccharose, none. Indol was produced in Dunham's peptone-salt solution. A slightly red pigment was observed in some of the cultures of this bacillus.

Strain 67 was derived from a colony on the aerobic blood-agar plates inoculated with unheated suspension of the same Specimen 19. The organism was an actively motile bacillus with rounded ends, about 4 microns long by 1.4 microns thick on the average. Variations in length between 2.4 and 6.2 microns and in thickness between 1.0 and 1.6 microns were observed. The flagella were peritrichous and apparently numbered from four to ten for each cell (this point was not satisfactorily ascertained). In gelatin stab cultures, it produced a funnel-shaped liquefaction resembling closely that produced by Strain 14 and Strain 35. In litmus-milk the reaction remained alkaline but there was slight coagulation after four days and some digestion of the casein apparent at this time but more definite subsequently. No gas was produced in fermentation-tube cultures of broth containing dextrose, levulose, lactose, maltose or saccharose. No indol could be detected in cultures grown in Dunham's peptone-salt solution. Fresh agar cultures were colorless, but later became orange in color. This strain corresponded in its various characters very closely to Strain 14 and, except for the pigment, it also agreed well with Strain 35.

TABLE 9—SUMMARY OF RESULTS OF AGGLUTINATION TESTS PREVIOUS TO JULY, 1911

	Positive Results					Negative Results				
	Strains					Strains				
	14	35	44	62	67	14	35	44	62	67
SERA OF NORMAL INDIVIDUALS										
Kerr	0	0	0	0	0	4	1	3	3	3
MacNeal	0	0	1	1	0	5	1	2	2	5
Guinea-pig	0	1	0	0	0	2	0	2	3	3
<i>Total</i>	0	1	1	1	0	11	2	7	8	11
SERA OF INSANE PATIENTS, NOT PELLAGRINS										
M. L.	1	2	0	0
B. N.	1	2	0	0
<i>Total</i>	2	4	0	0
SERA OF PELLAGRINS										
P. E.	2	1	2	1	2	1	0	0	1	0
M. Y.	1	1	1	1	0	0
M. G.	4	1	2	2	4	0	0	0	0	0
G. I.	1	1	1	0
T. E.	1	1	0	0	4	3	0	2	2	0
D. E.	1	..	1	2	1	0	..	1	0	1
W. N.	1	..	1	2	2	0	..	0	0	0
J. S.	1	..	0	0	0	0	..	1	1	1
E. P.	1	..	0	1	0	0	..	1	0	1
D. D.	1	..	0	0	1	0	..	1	1	0
A. D.	2	..	0	0	2	0	..	1	1	1
S. E.	1	2	0	0
J. N.	1	2	0	0
<i>Total</i>	18	5	7	8	20	6	0	7	6	4

In Table 9 are given in summary the results of agglutination tests on these five bacterial strains with the sera of pellagrins and various controls which were made prior to July, 1911, and the total number of positive and negative tests on the different classes of sera are seen to be as follows:

	Strain 14		Strain 35		Strain 44		Strain 62		Strain 67	
	+	—	+	—	+	—	+	—	+	—
Normal Controls	0	11	1	2	1	7	1	8	0	11
Insane Controls	2	0	4	0
Pellagrins	18	6	5	0	7	7	8	6	20	4

TABLE 10.—SUMMARY OF RESULTS OF AGGLUTINATION TESTS ON STRAIN 67 DURING JULY AND AUGUST, 1911

SERA OF HEALTHY INDIVIDUALS				
Individual	Residence	Remark	Positive Results	Negative Results
MaeNeal	Urbana	0	16 ¹
York	Urbana	15	0
H. E.	Urbana	3	0
H. D.	Chicago	0	3
M. Y. (C)	Chicago	0	2 ²
M. Y. (K)	Kankakee	1	0
Monkey 248	Kankakee	0	1 ²
Monkey 290	Kankakee	0	1 ²
<i>Total</i>			19	23
SERUM OF MONKEY FED ON CULTURES OF STRAIN 67				
Monkey 79	Kankakee		2	0
SERA OF PATIENTS NOT PELLAGRINS				
B. R.	Kankakee	Insane	0	1
M. R.	Kankakee	Insane	0	1
W. L.	Kankakee	Insane	1	0
P. N.	Kankakee	Insane	1	0
W. D.	Kankakee	Insane	0	1 ²
P. L.	Kankakee	Insane	1	0
J. S.	Kankakee	Insane	1	0
A. A.	Chicago	Sane, syphilis	0	1
R. Y.	Chicago	Sane, syphilis	0	1
B. I.	Chicago	Sane, syphilis	1	0
L. S.	Chicago	Sane, syphilis	0	1
C. K.	Chicago	Sane, syphilis	0	1
O. Y.	Chicago	Sane, typhoid	1	0
G. I.	Chicago	Sane, pneumonia	2	0
<i>Total</i>			8	7
SERA OF PELLAGRINS				
A. D.	Chicago	Sane	4	0
C. C. H.	Chicago	Sane	3	0
D. Y.	Chicago	Sane	9	0
G. M.	Chicago	Sane	2	3 ³
T. R.	Chicago	Sane	3	0
G. S.	Chicago	Sane	3	1
M. G.	Peoria	Insane	1	0
D. E.	Peoria	Insane	0	2
S. N.	Peoria	Insane	5	0
P. Y.	Peoria	Insane	1	0
B. N.	Peoria	Insane	3	0
C. N.	Peoria	Insane	6	0
B. R.	Kankakee	Insane	0	2 ²
S. E.	Kankakee	Insane ⁴	0	2
M. N.	Kankakee	Insane	6	0
<i>Total</i>			46	10

1. Four of these were slight agglutinations.

2. All of these were slight agglutinations.

3. Two of these were slight agglutinations.

4. Diagnosis of pellagra doubtful.

These tests directed attention particularly to Strains 14, 35 and 67, and especially to the last one.

In Table 10 is a similar summary of the results of the agglutination tests on Strain 67 with various sera, performed during July and August, 1911.

These results tend to break down the evidence suggesting that these bacterial strains bear a special relation to the disease pellagra, by showing that positive agglutination of them is frequently brought about by the sera of normal individuals and that the sera of pellagrins sometimes fail to produce this result. Some of these results, however, did support, in a way, the earlier evidence, especially the positive agglutinations of Strain 67 produced by the serum of every one of the acute typical cases of pellagra in sane individuals in the Cook County Hospital.

In the complete report the observations are set down in detail without any attempt to discuss the data. It is quite evident from a consideration of them that further experimental work is necessary before it will be possible to draw any important conclusions concerning questions in this field. The following conclusions are, at any rate, suggested by the observations and may be set down here in a tentative way:

1. In pellagra, especially in the acute attack, there are marked changes in the fecal flora as compared with the normal. Relative diminution in the number of bacterial cells per milligram of feces is frequently very great. The numerical relations of the different types of bacteria normally seen in the feces are disturbed, and in addition several new forms, more or less heterogeneous in nature, appear. Protozoa, amebae and flagellates are frequently present.

2. In cultures from the feces of pellagrins, various departures from normal relationships of the fecal bacteria are frequent, and many forms of bacteria occur which are not found in cultures of fecal bacteria of healthy men.

3. Three bacterial strains derived from three different cases reacted to agglutination tests with sera of pellagrins in a manner somewhat suggestive. These strains, 14, 35 and 67, were all derived from pellagrins at Peoria, but they were agglutinated by sera of pellagrins at Kankakee and at Chicago as well as sera of patients at Peoria. This somewhat suggestive evidence of a relationship to pellagra is refuted or very much weakened by the fact that these bacteria were also agglutinated by the sera of insane persons free from pellagra at Peoria and at Kankakee, and by the sera of apparently normal persons at Kankakee, at Chicago and at Urbana. Preliminary cultural investigation has suggested that two of these strains (14 and 67) are probably identical in nature, and that perhaps the other strain (35) is a closely related variety of the same species. They do not belong in the *B. coli* group.

4. Other bacterial strains which showed suggestive agglutination relations were all non-liquefying, gas-forming bacteria, probably closely related to *B. coli*.

2. *Protozoa*.

PEORIA

1. Protozoal infection among fifty non-pellagrous patients.

Number showing entamebas (26), 52 per cent.

Number showing flagellates (30), 60 per cent.

Of these fifty patients, eleven presented a definite and clear-cut clinical picture of amebic dysentery. Entamebas were demonstrated in 73 per cent. of these cases giving clinical evidence of dysentery, and in one case an amebic abscess of the liver was found at necropsy.

2. Protozoal infection among twenty-one pellagrous patients.

Number showing entamebas (16), 76 per cent.

Number showing flagellates (16), 76 per cent.

A further analysis of these statistics and comparison with clinical symptoms exhibited by each patient demonstrated the fact that of the twenty-one pellagrous patients five were suffering with dysentery resembling in all respects amebic dysentery. Entamebas were present in all five cases. Of the remaining sixteen cases, six presented diarrheic symptoms, and in five of the cases suffering from diarrhea entamebas were present. The remaining ten cases gave no evidence of either diarrhea or dysentery, but in six of these cases entamebas were present in the stools.

An attempt was made to classify the species of entamebas found in the patients at Peoria. The examination of fresh preparations was the routine method for all cases, but in many instances staining methods were used. The staining methods adopted were the following: polychrome stains (Leishman's, Wright's, MacNeal's, and Giemsa's) and the iron hematoxylin method of Heidenhain. It was possible definitely to establish the fact that at least three and probably four species of entamebas were present.

Entamæba histolytica was found in four cases.

Entamæba coli was present in a number of cases.

Entamæba tetragena. An entameba resembling in all respects the published descriptions of *E. tetragena* was found in some cases.

A number of preparations stained with polychrome stains and iron hematoxylin, and material containing encysted entamebas, were forwarded to Captain C. F. Craig, Medical Corps, U. S. A., for an expression of opinion. Captain Craig reported finding *E. coli*, *E. histolytica* and *E. tetragena*, thus confirming the findings of Captains Siler and Nichols.

It is quite evident that the most common form of dysentery at the Peoria State Hospital was due to amebas, for the following reasons: The typical clinical symptoms of emebic infection were present, pathogenic entamebas were present in the stools, and in many of the cases going to autopsy amebic ulceration or folliculitis was noted.

The flagellates found at Peoria were mainly *Trichomonas intestinalis*.

A statistical study of protozoal infection of the intestinal canal was undertaken among the patients (practically all non-pellagrous) at Kankakee and Dunning, without reference to the presence or absence of diarrhea or dysentery. The following results were obtained:

KANKAKEE

Examination of sixty-two patients.

Number showing entamebas (36), 56 per cent.

Number showing flagellates (48), 77 per cent.

No attempt was made to classify the types of entamebas encountered. The flagellates were, in the large majority of cases, *Trichomonas intestinalis*.

DUNNING

Examination of fifty patients.

Number showing entamebas, 46 per cent.

Number showing flagellates, 32 per cent.

At this institution, also, our time was limited and no attempt was made to classify the types of entamebas. In most instances, the organisms were "resting" or encysted. The flagellates were *Trichomonas intestinalis*.

The presence of entamebas and other protozoa, pointed out by Nichols and Siler in 1909, has since been exploited by several writers, notably Long, who carries his views to the extreme of considering pellagra a complication of amebic dysentery. We could find no support for such a view in our results at Peoria.

Careful stool examinations were also made of the patients occupying two cottages in which experimental corn and corn-free diets were instituted and carried out for a period of one year. A summary of the results of these examinations is as follows:

	Number of Patients	Cases Showing Amebas	Cases of Pellagra Showing Amebas	Cases of Pellagra Without Amebas
Corn diet	59	7	1	3
Corn-free diet	58	6	0	5

To add light relative to the extent of protozoal infection in the state hospital at Kankakee, Dr. J. T. Rooks examined a group of patients on admission and again at a later date. This study was made for the purpose of determining whether the infection took place after admission, and whether or not these organisms were pathogenic. Only a summary of Dr. Rooks' work is here appended:

TABLE 11.—PROTOZOAL INFECTIONS AT KANKAKEE

	No. of Cases	Amebæ Present				Flagellates		Amebas and Flagellates
		Active	Encysted	Total	Per cent.	Total	Per cent.	
First examination..	181	19	9	28	15.5	27	14.9	7
Second examination	104	21	..	21	20.2	23	22.1	7

Of the twenty-eight showing amebas at the first examination, only eleven were available for the later investigation and in these amebas were found only in three cases. At the second examination, amebas were found in eighteen cases which had previously given negative results. It should also be noted that where amebas and flagellates were found together these cases have been included also in the totals for the two types of organism given separately.

Attention was also paid to the relationship between the presence of amebas at the first examination and the action of the bowels, the results being given below in percentages:

No. of Cases	Normal Stools	Diarrhea	Constipation	Alternating Diarrhea and Constipation
28	75.0	10.7	7.1	7.1

The following conclusions, therefore, seem to be justified:

1. Of 181 recently admitted cases, 15.5 per cent. showed amebas in the stools, which apparently belonged to the group described as *E. tetragena*.

2. One hundred and four of these cases re-examined later showed 20.2 per cent. of amebas.

3. The percentage of infected individuals apparently increased with the term of residence in the Kankakee State Hospital.

4. In all probability the majority of these organisms are non-pathogenic.

BLOOD

Results of blood examinations in pellagra have been published by many different authors without the demonstration of any changes which are in any way constant or characteristic. Points which have chiefly been emphasized in regard to the cytology are the occurrence of a high

TABLE 12.—RESULTS OF BLOOD EXAMINATIONS

	Age	Yrs. in Hospital	Red Cells per c.mm.	Hemoglobin in gm. per cent.	Color Index	White Cells per c.mm.	Per Cent.						
							Polymorphon. Neutrophils	Small Lymphocytes	Large Lymphocytes	Mononuclear Leukocytes	Transitional Cells	Eosinophils	Basophils
I.	62	8	4,248,000	13.44	1.12	12,500	39.8	12.6	17.0	25.0	1.0	4.0	0.6
S.	44	19	4,696,000	16.86	1.27	8,160	65.2	10.4	11.2	9.2	1.6	2.2	0.4
.....	56	19	4,845,000	15.88	1.15	10,540	59.0	18.8	9.4	6.8	2.2	2.8	1.0
.....	45	24	5,442,000	17.3	1.13	8,250	55.8	15.2	14.4	5.8	1.6	7.0	1.0
.....	50	12	5,836,000	16.8	1.02	11,380	60.0	14.8	11.6	9.8	1.0	2.6	0.2
.....	52	19	5,036,000	13.92	0.98	8,120	63.8	14.8	10.2	8.0	1.8	1.2	0.2
.....	60	39	4,800,000	13.92	1.03	12,200	54.0	13.6	12.2	17.2	1.8	2.0	1.2
.....	46	26	2,566,000	10.26	1.11	10,400	66.4	17.0	11.6	1.0	0.4	1.2	1.4
.....	68	8	4,936,000	12.96	0.94	7,280	62.6	12.2	11.0	10.6	1.2	1.8	0.6
Y.	39	12	6,016,000	16.8	1.00	10,640	56.0	14.4	6.8	11.4	2.0	8.8	0.6
.....	72	25	4,640,000	14.40	1.04	7,440	58.2	12.0	8.0	11.4	3.0	6.6	0.8
.....	45	25	4,816,000	12.44	0.91	10,840	63.2	10.2	7.6	10.0	1.4	7.2	0.4
.....	55	18	4,528,000	11.04	0.87	13,800	65.2	11.4	7.6	10.4	3.4	1.4	0.6
.....	62	12	5,848,000	14.40	0.88	6,800	73.8	8.0	5.0	8.0	3.2	1.8	0.2
.....	38	7	6,288,000	15.36	0.85	11,440	78.2	6.4	3.8	3.6	4.0	3.2	0.8
.....	36	14	4,220,000	12.44	1.06	12,960	75.0	9.0	4.4	7.0	2.8	1.2	0.6
.....	50	21	4,696,000	13.92	1.05	13,700	71.4	9.8	6.0	6.2	4.6	2.0	0.0
.....	43	7	4,116,000	12.00	1.04	8,380	67.6	11.6	7.8	6.0	5.8	0.4	0.8
.....	23	3	4,880,000	12.44	0.91	8,160	50.0	11.0	7.0	18.6	9.4	3.4	0.6
I.	63	21	4,496,000	11.52	0.94	10,720	76.8	6.2	3.2	6.5	3.8	2.6	0.8
.....	74	1	4,352,000	11.52	0.94	13,120	57.0	22.0	3.0	9.6	6.0	1.8	0.6
.....	52	14	4,992,000	12.96	0.92	9,200	65.0	13.8	7.2	8.6	2.8	2.4	0.2
O.	46	18	4,328,000	11.04	0.91	15,000	56.0	10.4	5.2	20.4	0.0	4.0	1.2
.....	44	9	5,048,000	13.92	0.98	12,140	70.2	11.0	8.4	7.4	1.2	1.8	0.0
.....	66	2	6,080,000	12.00	0.71	7,860	41.6	18.8	8.4	16.4	6.0	7.0	1.8
age	51	15	4,872,000	13.62	0.99	10,416	61.7	12.6	8.4	10.2	2.7	3.2	0.6
imum	74	39	6,288,000	17.3	1.27	15,000	78.2	22.0	17.0	25.0	9.4	8.8	1.8
mum	23	1	2,566,000	10.26	0.71	6,800	39.8	6.2	3.0	1.0	0.0	0.4	0.0

color-index and an increase in the proportion of mononuclear leukocytes. Leukocytosis has occasionally been observed but as a rule is absent. In reading the results of blood counts on most of the cases examined in this state it must be remembered that we are dealing, in the main, with individuals who were not normal before the onset of the pellagra. Blood changes are found in many of the chronic insane and this fact should be borne in mind in considering the examinations of such individuals who subsequently become pellagrins.

TABLE 13.—BLOOD EXAMINATION OF PELLAGRINS DURING THE ACUTE OR SUBSIDING STAGES

	Red Cells per c.mm.	Hemoglobin, gm. Per Cent.	Color Index	White Cells per c.mm.	Per Cent.							
					Polymorph. Neutrophils	Small Lymphocytes	Large Lymphocytes	Mononuclear Leukocytes	Transitional Cells	Eosinophils	Basophils	Unclassified
J. B.....	4,088,000	11.52	1.0	7,400	54.20	28.33	5.66	4.21	0.59	5.59	1.22	0.19
N. A.....	5,032,000	10.56	0.76	6,620	69.6	14.07	10.2	2.22	1.11	1.16	0.37	0.0
C. G.....	4,205,000	11.52	1.0	6,400	47.33	33.83	10.5	3.17	0.33	2.00	1.16	0.0
J. S.....	5,200,000	12.0	0.82	9,000	60.43	25.96	4.3	1.37	0.58	7.0	0.19	0.0
C. A.....	3,960,000	11.5	1.3	9,600	64.46	29.15	3.2	0.0	0.0	2.96	2.3	0.0
J. S.....	3,652,000	10.06	1.0	7,600	66.0	21.0	6.0	2.4	1.5	3.1	0.0	0.0
E. S.....	4,664,000	13.9	1.06	7,400	61.43	20.28	12.6	2.57	1.86	1.0	0.29	0.0
J. N.....	5,120,000	9.6	0.7	7,200	31.78	34.68	17.1	1.36	1.16	13.4	0.58	0.0
	4,542,000	9.6	0.76	7,000	38.0	50.4	4.8	6.8	0.58	0.0
	4,682,000	10.8	0.8	7,200
J. V.....	4,640,000	16,920	78.0	15.0	0.0	5.0	0.0	2.0	0.0	0.0
Average.	4,524,864	11.1	0.97	8,394	57.22	34.22		3.42		4.5	0.67
Maximum	5,208,000	13.9	1.3	16,920	78.0	51.78		5.0		13.4	2.3
Minimum	3,632,500	9.6	0.7	6,400	31.78	24.27		0.0		1.0	0.0

With this in view it was thought well to tabulate for comparison the blood findings in a group of individuals suffering from chronic mental disorder and comparable in that respect with the great majority of available pellagrins. They include cases of senile dementia, dementia præcox and defective mental development. The results of twenty-five such examinations performed by Dr. Addison Bybee, late clinical pathologist to the Psychopathic Institute, are given in Table 1. These cases were selected for the reason that in age, type of mental disorder and long residence in hospital they fairly correspond with the bulk of the population of the Peoria State Hospital.

It will be observed that in twelve of these the color index is normal or slightly above in spite of the fact that some of these show a diminished number of red cells. The two cases presenting the smallest number of red cells, viz., 2,566,000 and 4,116,000 have, respectively, a color index of 1.11 and 1.04. With regard to the proportions of the different varieties of white cells it will be seen that on an average also the relative number of large mononuclear leukocytes and transitional cells is somewhat high. Attention should be called to the presence of eosinophilia in several of the cases.

In Table 13 will be found the results of eleven examinations made on nine different patients during the acute or subsiding stages of pellagra.

It will be observed that in five of these the color index is at or slightly above the normal, although in all five the number of red cells is more or less subnormal. In only one patient, J. V., was there any leukocytosis. This patient, reported in more detail below (Case 2), was apparently not insane before the onset of pellagra. The number of leukocytes increased at subsequent examinations from 16,920 to 20,480 per c.mm. The attack was very severe, with fatal result, and at necropsy no evidence of any septic focus was found to account for the leukocytosis with absolute and relative increase in the polymorphonuclear leukocytes. One must therefore conclude that this was due to pellagra. Apart from this case all other patients have shown a relative lymphocytosis and there is apparently a diminution in the proportion of large mononuclear leukocytes. It will be observed that the increased number of lymphocytes was not limited to the larger varieties, so that it cannot be explained by differences in nomenclature and a confusion between large lymphocytes and large mononuclear leukocytes. Eosinophilia is also present in five of the nine cases. In one of these patients, J. N., the proportion is as high as 13.4 per cent. and it may be noted that this patient also showed amebas in the stools. The eosinophilia, however, does not always correspond with amebiasis as, for instance, in J. B. no amebas were found. In view of the findings in Table 7, however, one need not be surprised at these figures.

A blood count of the patient, J. N., made eighteen months after the disappearance of all pellagrous symptoms at a time when the patient was apparently in good health and had had no recurrence, gave the following results: Red cells, 4,720,000 per c.mm.; hemoglobin, 11.5 per cent.; color-index, 0.87; white cells, 8,200 per c.mm., of which 50.5 per cent. were polymorphonuclear neutrophils, 42 per cent. lymphocytes, 1.5 per cent. mononuclear leukocytes and transitional cells, 5 per cent. eosinophils and 1 per cent. basophils.

Besides these enumerations several weeks were occupied in the careful study of blood both in the fresh state and after staining by various

methods. The fresh blood was examined with direct illumination and the dark-field illuminator. The stains employed have been those of Jenner, Giemsa, Levaditi and methylene blue. In no specimen has anything been observed which seemed to be in any way abnormal.

Cultures were made from the blood in several cases with negative results, except in one instance, J. N., at the Kankakee State Hospital. In this case a large motile bacillus was obtained which grew freely but somewhat slowly on all media. That it was not a contamination seemed to be proved by the fact that the organism was agglutinated by the patient's serum. No clumping was obtained, however, with the sera of other pellagrins or healthy individuals and the bacillus gave no evidence of pathogenicity even in large doses when injected into a monkey and a guinea-pig. We are therefore inclined to regard this as evidence only of a lowered resistance to the invasion of the individual by parasites.

Similar investigations carried out at Peoria by Captains Nichols and Siler gave results which are reported by them as follows:

Blood cultures and spinal-fluid cultures were made from ten living cases, and cultures from the spleen were made in six cases at autopsy. In every instance the results were negative.

The greater portion of two weeks was devoted to the examination of fresh blood and spinal fluid, and smears from the blood, spleen, and liver. The smears were stained with the Leishman ptychrome stain, with Giemsa's polychrome stain, and with Mac Neal's polychrome stain. Nothing whatsoever suggestive of a protozoal infection was encountered.

Blood cultures were made on blood-agar (trypanosome media), the results in each instance being negative.

URINE

Specimens have been examined repeatedly from the patients transferred to Kankakee from Peoria and also in cases arising in the former institution. No constant changes have been found with the exception of a very marked indican reaction which was present in all and can probably be correlated with the intestinal putrefaction. In a few instances a trace of albumin and a few hyaline casts have been present.

One striking feature also has been the great variability in quantity, color and specific gravity of the specimens obtained on various days from the same patient. In the case of J. N., who passed through a very severe attack, these variations were remarkable and are recorded in graphic form on Chart 2. It should be stated that the estimations of chlorids, phosphates and sulphates were made by the Purdy centrifuge method and hence cannot be regarded as accurate. Nevertheless, since they were all made with the same centrifuge revolved for the same length of time, a comparison between the readings for the different days

is quite permissible. These results cannot be regarded as indicating anything more than evidence of great disturbance in metabolism and suggest the advisability of more exact study of the exchanges.

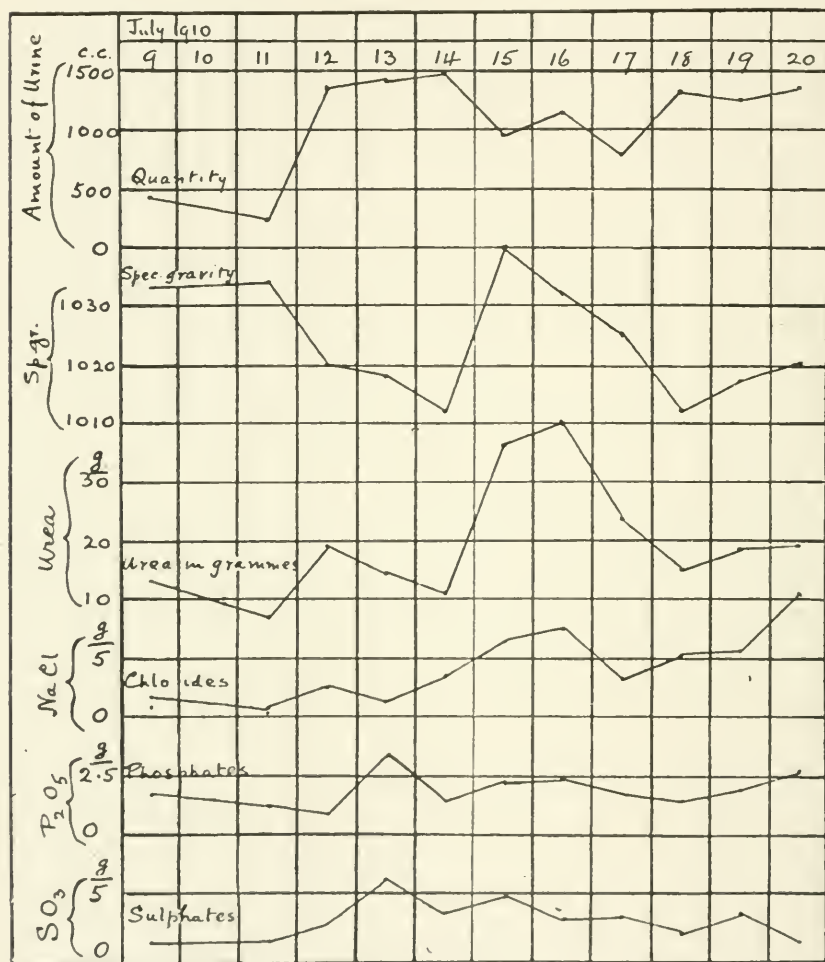


Chart 2.—Showing variation in quantity, color and specific gravity of urine on different days in the case of J. N.

THE COURSE OF THE DISEASE

The great majority of cases have shown an acute course with sudden onset and have arisen for the most part in individuals of poor physique, although some few have been well nourished and apparently healthy. As a rule the earliest symptom observed has been the skin eruption on the hands with simultaneous or rapidly succeeding soreness of the mouth and more or less diarrhea. This acute phase lasts for one or

two weeks and then gradually subsides with the replacement of the erythma by a thickened, dry, scaly condition of the skin which may last several weeks or even months, during which desquamation occurs.

A certain proportion of the cases have begun with gastro-intestinal symptoms, consisting of chronic and often severe diarrhea with more or less stomatitis. At this stage the diagnosis is very difficult to make and cases have been observed in which these symptoms have been present for one or two months before the appearance of the characteristic rash. The eruption has appeared suddenly and has generally been very severe with marked bleb formation and ulceration. These cases, in our experience, have been extremely fatal, the patient rapidly losing flesh and becoming weaker. We are inclined to regard the occurrence of severe mouth symptoms in any case as of very grave import. Nevertheless in some cases in which death has seemed to be only a question of a few days, improvement has occurred with an apparently complete recovery. One such example, J. N., at the Kankakee State Hospital, where death was momentarily expected in the spring of 1910, made a good recovery and has had no recurrence up to November, 1911, being apparently in fully as good health as before the attack. This patient, though not robust was nevertheless in a good state of nutrition and health before the onset of the pellagra.

Another form of course deserves to be especially mentioned because it touches on the important question as to what constitutes pellagra and when it may be considered as recovered. In these cases the gastro-intestinal symptoms are usually severe and there is consequently progressive emaciation and exhaustion. After a few weeks the skin lesions disappear and the mouth may get well, diarrhea becoming less or even disappearing, and yet the patient does not improve or only slightly and then temporarily. Without any recurrence of the acute symptoms of pellagra there is a gradual decline with increasing evidence of involvement of the nervous system until the picture becomes unmistakably that of central neuritis which ends fatally in a short time (See case J. V. below).

In some instances these symptoms have occurred within a few days of the subsidence of the characteristic pellagrous phenomena or even while they are still present, whereas in others they have been delayed for several months. We do not feel justified in expressing any definite opinions on the meaning of this condition but it may be suggested that the sequence is somewhat similar to that which occurs in diphtheria in which a peripheral neuritis follows at a longer or shorter interval after the actual infective agent has been eliminated. Yet it is unquestionably due to the action of the toxins, produced by the organisms, on the peripheral nervous system. In pellagra the

neuritis is more particularly central, but may well be a late effect of the toxins, whatever their nature, as in diphtheria, and does not necessarily indicate that the disease is still active. Progressive emaciation and exhaustion after the subsidence of the characteristic manifestations of pellagra, have been noted by many authors and have been regarded by some as evidence that the disease is still active. We are unable to say whether all such cases present symptoms of central neuritis or not, as the necessary data are not available. Attention to this point is certainly desirable, as it offers the possibility of a definite explanation for this otherwise puzzling course.

It is usually stated that in most cases after the subsidence of an attack the patient regains his health more or less completely and may seem to be entirely recovered, but with the appearance of the next spring or autumn there is a recrudescence of the active symptoms. The short time during which cases have been under observation in this state renders it impossible to give any very reliable data concerning this question, but it may be stated that many of the patients showing attacks in 1909 and 1910 have not presented any recurrence up to date, although they have been closely watched. The actual figures are given in the statistical study. Of the six cases transferred from the Peoria to the Kankakee State Hospital in July, 1910, selected for the reason that they presented unquestionable symptoms of pellagra, none up to the end of November, 1911, have shown any further symptoms of the disease. (One of these patients died from pneumonia April 15, 1911.) The best marked example of annual recurrence was seen in the city of Peoria by the courtesy of Dr. J. H. Bacon,² as already referred to. This patient had had seven attacks in seven years although the diagnosis was not made until the seventh and fatal attack in March, 1910.

Finally there are to be mentioned cases which present a much more chronic course as regards the individual attacks. In these cases there is, as a rule, but little constitutional disturbance and the initial erythema is slight or may not be seen at all. There occurs, however, a slowly increasing pigmentation with some thickening and roughness of the skin of characteristic distribution, symmetry and outline. The color in these cases becomes extremely dark, often almost black, and persists for some months, when desquamation occurs and the skin gradually resumes a more normal color. This condition has only rarely been observed among the cases in this state and is perhaps more difficult of diagnosis, especially when it occurs in old people, than the more acute forms.

PATHOLOGICAL FINDINGS

The post-mortem findings in so far as they have yet been worked up are described in detail below in connection with the descriptions of the cases. While it cannot be said that there is anything specific about the

changes found, yet there are certain features which seem to be constant and open up certain more or less definite lines for future search. These may be summarized as follows:

1. The *nervous system* presents a picture of axonal chromatolysis involving especially the Betz and larger pyramidal cells of the precentral convolutions and the cells of the nuclei in the cerebellum, pons, medulla and cord as well as the posterior root and sympathetic ganglia. Besides these changes numerous cells in most cases show a marked pigmentary degeneration of fatty nature similar to that found in the senile nervous system and in some other conditions. With this there is, in most cases, but little evidence of connective tissue reaction, and we would especially emphasize the absence of infiltration of the perivascular sheaths. In some cases there is more or less overgrowth of glia cells along the vessels and around the nerve cells. The picture here described is identical with that published by others, notably Spiller and Anderson, in cases of pellagra, but is also strikingly similar to the picture of central neuritis. This similarity, indeed, led us to ask whether the patient did not have the clinical picture of that condition before we were aware that Dr. Wilgus, superintendent of the Elgin State Hospital, had already observed and commented on it.

Central neuritis, like peripheral neuritis, must not be regarded as a disease *sui generis*, but merely as a type of reaction on the part of the nervous tissue, capable of being produced by various harmful agents. In response to a letter, Dr. Adolf Meyer, who first described the changes which bear this name, writes that he is not surprised to hear that they are found in the end stages of pellagra and gives the interpretation contained in the above words.

2. The *liver* has been constantly the seat of small islets of a low-grade inflammation of the portal connective tissue lying in the interlobular septa. The intralobular capillaries are engorged and in most cases there are many small blood extravasations. The liver cells have undergone fatty degeneration which is in some instances remarkable, and the change is distributed in every case along the periphery of the lobule. This, in the absence of any marked cirrhosis, at once suggests that there may have been some toxin circulating in the portal blood-stream. Some of the specimens even suggest a picture of a very early stage of acute yellow atrophy or the more acute forms of alcoholic cirrhosis.

3. *Intestinal* ulceration has been present in three out of seven cases. This has not the acuity of an amebic infection and no amebas have been found in the walls. Even where no ulceration was found a low-grade infiltration of the mucosa and submucosa has been present in places.

These findings are certainly of interest in relation to the condition of the liver.

4. The *kidneys* show degenerative changes in the renal epithelium and in all cases more or less interstitial nephritis, in spite of the fact that the ages in some of the cases is certainly not great. Engorgement of capillaries with small hemorrhages are also frequent.

5. The *spleen* shows some fibrous overgrowth and again small hemorrhages.

6. Pigmentary changes are present in the *heart muscle* at an age which is below that at which they are usually found.

7. In some of the cases hyaline changes in the intima of the blood-vessels has been marked, but this is not constant.

All these appearances suggest the presence of some toxic substance in the blood. One may even go further and from the changes in the intestine and especially in the liver, suspect that this toxin originates in the intestine and enters the circulation by way of the portal system. The great frequency of gastro-intestinal symptoms during the clinical course of the disease might be regarded as pointing in the same direction. There is always, however, to be borne in mind the possibility that these changes may be secondary to the pellagra. That is to say, that as the result of the gross disturbances in metabolism and vital resistance, which certainly accompany the disease, there may follow a secondary invasion of the intestinal tract with organisms which then give rise to the changes found by virtue of the toxins elaborated during their growth. Secondary changes such as this would be quite in accordance with what is found in other diseases.

If, however, we look for evidences of the localization of a blood-borne parasite in other parts of the body we find entirely negative results. The nervous system does not present any features similar to those found in such diseases as trypanosomiasis or parasyphilis. The absence here of any focal changes and of perivascular infiltration are strikingly different from the conditions found there. The picture presented is much more that of a diffuse toxic state than of one due to a blood infection. The only tissues in which there seemed to be any focalization of lesion were in the intestinal wall and the liver. In this latter organ the areas of infiltration present in the interlobular septa were decidedly local and often widely separated, and where found, existed in the form of more or less circular islets. There was no generalized invasion of the whole of the connective tissue. The intensity of the infiltration was certainly of low grade and did not suggest a very acute inflammation.

As already indicated, the study of degeneration in the nervous system is very incomplete, but from what has been seen so far there is no evidence

of any system degeneration. The fibers in the cord which stain by the Marchi method are scanty and widely scattered and there is nothing to support the suggestion made by Long that the nerve roots are pressed on as they pass through the intervertebral foramina. It might also be mentioned that the distribution of the skin lesions does not correspond with that of the posterior roots of the cord. The perfect symmetry so characteristic of the skin lesions in pellagra is hardly conceivable as the result of any gross nervous lesion and suggests far more some generalized noxious agent which is capable of a far finer biochemical selective power than could possibly be conceived from pressure or other gross lesion of like kind.

Pellagra is sometimes described as a disease especially involving the nervous system. From the findings here described the nervous system seems to be involved only as a secondary process and at a late stage of the disease, in this respect confirming the opinion expressed above from clinical study.

Without expressing any opinion as to casual relations, it seems to us that the main indications revealed by the pathological study point to the need for closely following up investigations on the intestinal tract. At the same time we can admit that this *habitat* would not contradict the hypothesis that the parasite has entered the system through the blood stream as the result of bites by insects.

CASE REPORTS

CASE 1.—Pellagra in a Previously Healthy Woman Which Without Improvement in the Specific Symptoms Led to Death in Three Months.

History.—A. D., a white female, aged 43, seamstress by occupation and a widow. She is said to have been a healthy woman, though always in poor circumstances and during the last few months has had a hard struggle for existence. She has four living children and had one stillbirth but no miscarriages. The menopause occurred five years ago. Her only illnesses during adult life have been gonorrhea "several years ago" and malaria "on several occasions." She had been living in Corinth, Mississippi, for "several years" until June, 1910, when she came to Chicago, where she has been since. Previous attacks of pellagra are denied.

Present Illness.—Present illness began in October, 1910, the first symptoms being "chapping of the hands" with diarrhea and progressive emaciation. The hands became raw and fissured and this was accompanied by pain of a burning character. Diarrhea has been very profuse and for two months there had frequently been blood in the stools, sometimes in the form of clots. The mouth also became very sore, rendering eating difficult and there was profuse salivation. In spite of this she showed a craving for food, the ingestion of which would often give rise to "cramps." No definite mental symptoms have been noted with the exception of a change in temperament, in that she was more fretful and irritable than usual. At no time has there been any evidence of "wandering in her mind."

Examination.—She was admitted to the Cook County Hospital Jan. 12, 1911, under the care of Dr. W. A. Pusey, to whose courtesy we are indebted for permission to use this case. At this time she presented an extremely emaciated condition with incessant diarrhea. Mentally she was clear and remained so until

the time of her death, but was listless and apathetic. Some degree of depression was present but this did not seem to exceed the limits justified by her condition. She answered questions clearly and readily and her memory seemed to be good, although the examination was not very thorough.

On the backs of the hands extending upwards to about 2 inches above the wrists and forming a cuff around the wrist was a characteristic pellagrous eruption completely symmetrical on the two sides. The skin over this area was deeply pigmented, fissured and excoriated, with yellowish exudate between the roots of the fingers. The mucosa of the lips, tongue and inside the cheeks was markedly red, swollen and partially denuded, with yellowish exudation where the lips came in contact with the teeth.

The diarrhea continued with great severity, accompanied sometimes by the passage of blood and the patient rapidly became weaker. She was first seen by us on Jan. 20, 1911, at which time she was so weak and ill that an exhaustive examination was not permissible. She rapidly became tired when talked to, the swelling of the mouth and tongue rendering it difficult for her to converse. She, however, seemed to be clear and gave some details concerning her illness without hesitation or error. She was not unduly depressed but realized that she was dying and was very willing to permit any examination which would help to elucidate the disease which she recognized as being somewhat rare. The knee-jerks were greatly exaggerated but equal on the two sides, yet did not appear to be more marked than is commonly found in advanced exhaustion. The plantar reflexes were both of flexor type. Rough testing revealed no gross changes in sensibility of the skin.

Blood was taken by venipuncture for agglutination and complement fixation tests. The stools were also examined for amebæ but none were found.

Necropsy.—Death occurred Jan. 22, 1911, at 1:30 p. m. and an autopsy was performed the following day at 11 a. m. At this time the pellagrous eruption was still well-marked and the evidences of excoriation in the mouth were quite distinct. On section the lungs showed considerable edema, especially at the bases. There was a healed calcareous sear at the right apex, but otherwise no change. The pericardium contained some excess of clear fluid but the heart and vessels showed no notable changes. The heart muscle was somewhat thin and flabby and there was no hypertrophy of the left side.

The kidneys showed some evidences of early chronic interstitial nephritis. The adrenal bodies were firm, each weighing 4 g.

The spleen was larger than normal (weight 200 gm.) and its substance seemed to be unduly firm, but there was no evidence of great increase in fibrous tissue.

The intestinal tract appeared normal everywhere with the exceptions of the mucosa of the mouth and the lower part of the sigmoid flexure in which were found about ten small, roughly circular, ulcers from 2 to 8 mm. in diameter. These ulcers were all situated within a length of about 2 inches. The edges were somewhat heaped up but not undermined. The surface was rough. The mesenteric glands were also enlarged but on section showed an approximately normal appearance.

The liver was engorged with blood and its section showed an obviously fatty appearance.

The pelvic organs presented nothing abnormal but the mucosa of the vagina was very red and somewhat swelled, especially in the region of the fornices.

The central nervous system presented no very definite changes, with the exception of some increase of fluid over the convexity of the brain.

Portions of all organs were removed for microscopical examination, and one hemisphere of the brain was sent to the University of Chicago for chemical examination by Dr. Waldemar Koch.

MICROSCOPICAL EXAMINATION

Lungs: The lungs show nothing abnormal beyond general extreme congestion.

Heart: Heart muscle shows no increase in fibrous tissue. The blood vessels are engorged and here and there are to be seen small extravasations between the

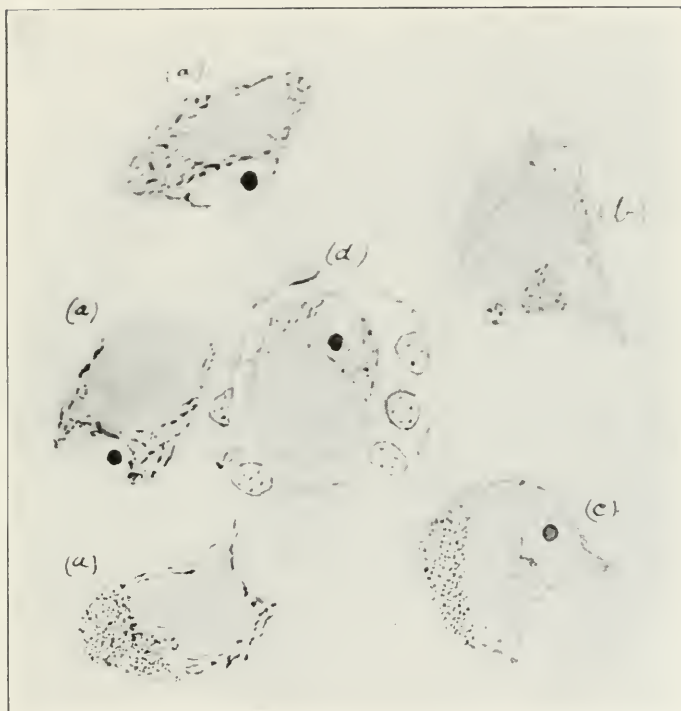


Chart 3.—Case A. D. Nerve cells showing chromatolysis and pigmentary changes; (a) from Clarke's column, (b) from ant. central convolution, (c) from ant. corn in cervical region, (d) from post. root ganglion.

muscle columns. The muscle cells stain diffusely with a granular appearance. In places vacuoles are found within the cells and in many of them there are small collections of greenish-yellow pigment around the nuclei. The muscle cells also show a tendency to fragmentation.

Kidneys: The capsule is moderately thickened and there is some increase of fibrous tissue between the tubules and also of Bowman's capsule. There is marked congestion of the vessels, especially in the medullary rays, with here and there small hemorrhages which are more numerous close beneath the capsule and in the medullary rays. The cells of the convoluted tubules are swollen, granular, and their outline is indistinct, while their nuclei stain rather poorly as compared with those of the smaller tubules. The glomeruli are congested but well stained and show no changes in the vessel walls. There is no denudation of epithelium. There is a moderate amount of small round-celled infiltration close beneath the capsule but this is not noticeable elsewhere.

Spleen: Moderate overgrowth of connective tissue involving the capsule and trabeculae. The pulp is engorged with blood and there are a few small areas in which the blood cells are undergoing disintegration, which probably represent small hemorrhages.

Suprarenal Glands: The cells in the glomerular layer are well stained but show small vacuoles of fat which become more marked in the fascicular layer. The vessels are all engorged, especially in the fascicular layer where there are several minute hemorrhages. A similar appearance is observed in the reticular layer. The central veins are widely dilated.

Liver: The capsule is slightly thickened and there is a very moderate increase of fibrous tissue in the portal canals. In this latter there is also an infiltration with small round cells, moderate in degree. The blood vessels are extremely dilated and this dilatation becomes greater as the capillaries approach the central veins of the lobules, in many places the width of these capillaries being greater than that of the liver cell columns themselves. Close beneath the capsule there are a number of small extravasations of blood. The parenchyma is well stained but there is marked fatty degeneration of the cells around the periphery of the lobules, many of the cells appearing to consist of a large fat droplet. In some lobules there is also fatty degeneration of the cells near the center, although this is nowhere very marked. The bile-ducts are well stained and not increased.

Pancreas. The pancreas shows a marked engorgement of the blood-vessels with very slight increase in fibrous tissue, but otherwise no change.

Intestinal Ulcers: Serial sections made through one of these ulcers showed a somewhat subacute type of inflammation with increase of fibrous tissue elements and moderate small-celled infiltration. A careful search was made for the presence of amebas in the ulcer wall and sections were submitted to Captain Nichols of the Army Medical School, Washington, D. C., who examined them in collaboration with Dr. Neate, microscopist to the Museum of the Army Medical School. They report that they "have been unable to satisfy ourselves that they contain any amebas. The general picture, too, does not seem to be active enough for an amebic ulceration."

Besides the ulcers, similar infiltrations of the submucosa and even deeper than the muscularis mucosae were found in the apparently healthy wall of the intestine.

Mesenteric Lymph-Nodes: These on section showed marked engorgement of the vessels with blood and some dilatation of the lymph-spaces but there appeared to be no increase of connective tissue and no other pathological changes.

Sections of the *ovary* and *tonsil* revealed nothing worthy of special note.

Central Nervous System: The pia mater showed no changes either with regard to its connective tissue or blood vessels.

Nerve Cells (Fig. 3): Sections were examined from various regions of the cortex and also from different levels in the cord and medulla. Stained with methylene blue and cresyl violet, marked chromatolytic changes of an axonal type were found in the large pyramidal cells of the Rolandic region but especially of the Betz cells. Of these latter practically all show extreme changes. The

cells are swollen and stain faintly, the nucleus is displaced and the nucleolus often stains poorly. The Nissl granules have largely disappeared, small collections of them remaining at the base of the larger processes, along the edges of the cells, and often collected as a small mass around the nucleus. Very many of these cells show masses of a yellowish green pigment, sometimes almost filling the larger part of the cell. This pigment stains black with osmic acid. The large pyramidal cells show somewhat similar changes, especially in regard to the pigmentation; but the chromatolytic changes are not so marked and many healthy cells are still present.

In other regions of the cortex an occasional larger pyramidal cell is found showing evidences of chromatolysis but they are nowhere very marked. The Purkinje cells of the cerebellum show generally a somewhat poor content of chromophil granules but are not otherwise changed. The dentate nucleus shows many cells with chromatolysis.

In the medulla oblongata the cells of practically all nuclei show marked chromatolytic and pigmentary changes, especially in the larger types of cells.

In the spinal cord similar changes are found in some anterior horn cells at all levels examined, but the great majority of these cells appear healthy. The most marked changes were found in the cells of Clarke's column where the majority of them were undergoing chromatolysis and pigmentary degeneration. Chromatolytic changes were also found in the cells of the posterior root ganglia. In specimens stained by the Marchi method the pigment deposits both in anterior horn and Clarke's column cells are very evident.

Marchi Method: Brain sections by this method have not yet been studied but in the spinal cord there are a few degenerated fibers scattered diffusely through the white matter. This does not especially involve the pyramidal tracts. Degenerated fibers are also present in both anterior and posterior spinal roots.

Glia and Vessels: The absence of any increase of glia cells is very striking. Not more than one or two satellite cells are found in relation with the degenerated cells, and the glia nuclei are nowhere more numerous than normal except possibly around some of the larger vessels. The cerebral vessels show in places a slight increase of the adventitial nuclei but there is absolutely no infiltration of the perivascular sheaths. This is true in all sections examined and certainly forms a striking contrast to the pictures seen in syphilis, parasymphylis and trypanosomiasis.

Attention may also be called to the large number of corpora amylacea which are present in the spinal cord, situated especially along the course of the postero-lateral septa and along the borders of the anterior fissure. In these regions as many as ten or twelve may be seen in the field of a 4 mm. objective. When the age of this patient (43 years) is considered the pigmentary changes and corpora amylacea must be regarded as definitely pathological.

Chemical examination of the right cerebral hemisphere by Waldemar Koch, Ph.D., of the University of Chicago showed a diminution of the neutral sulphur fraction without change in the total sulphur. Such a condition as this has been found hitherto only in the brains of individuals who have suffered from dementia precox. There was no change in the phosphorus content.

CASE 2.—*Pellagra in a Patient of Psychasthenoid Personality Accompanied by Disorientation, Perplexity and Some Anxieties with Hallucinations. Generalized Eruption One Month After Onset. Disappearance of Active Pellagrous Symptoms and Simultaneous Mental Improvement But Without General Recovery. Development of Central Neuritis Two Months Later. Death Four Months After Onset.*

J. V., white female, housewife, aged 57, married.

Family History.—This was meager, but showed nothing of importance.

Personal History.—Information concerning her early life was not obtainable. Within one week of her marriage at the age of 29 she was noticed to have psychasthenoid symptoms. She has had a very hard life, having to assist in earning a maintenance for her family of four children. Her husband left her in 1905 to take up some land in Wisconsin, the patient after much querulous hesita-

tion refusing to live there with him, not because there was any quarrel but because she could not stand the desolate surroundings. During the whole of her married life she was irritable, unable to make up her mind to do things and would worry over them when they were done. Such hesitation and indecision have characterized all her acts, even in relation to minute details, such as cooking food, etc.

She has lived at Mazon in Grundy County, Illinois, ever since her marriage, with the exception of a short visit to her husband in Wisconsin and to a daughter in Kansas City, Missouri. She returned from this latter trip about December, 1909, and has been living in Mazon since. She has been a semi-invalid for many months and was operated on in October, 1910, for a fistula and ischio-rectal abscess. She was more irritable and unable to make up her mind during this time than before but there were no other definite evidences of mental disturbance.

No history of any eruption suggestive of an attack of pellagra in the past could be obtained.

Present Illness.—At the end of April, 1911, she developed an "eczema" of the hands with severe diarrhea and about the same time she seemed to go "out of her mind." She did not know at times where she was and spoke of seeing smoke around the house. She recognized people, however, and seemed better when visiting in other homes than she did in her own. She became rapidly weaker, more fretful and seemed more dazed. No evidences of apprehension or further hallucinosis were noticed.

Physical Examination.—She was admitted to the Kankakee State Hospital May 13, 1911, when she was found to be much emaciated, with a well-marked pellagrous eruption on the hands, severe diarrhea and raw, swelled tongue with much gingivitis.

Physical examination revealed no signs of other disease. The reflexes were increased equally on the two sides, the plantars being of flexor type. All movements were very feeble and there was some tremor of the fingers.

Mental examination showed her to be depressed and somewhat clouded. She was very restless and seemed anxious and worried. She mistook nurses for people whom she had known before, and answered most questions with "I don't know." She performed a number of acts of perplexity, such as pulling off her bed clothing and piling it on the floor, and she wandered about in a dazed manner. The pellagrous eruption on the hands was of extremely dark color, some fissures were present about the knuckles and desquamation was marked at the time of admission. The eruption rapidly disappeared, desquamation being practically complete by the middle of June, leaving a pink, rather delicate looking skin. The sore mouth also improved and was well in about one week after admission. Diarrhea was severe during May but disappeared after that time, when she became more or less constipated, with only one day in which there were four stools which could not be accounted for by purgatives.

May 23, 1911, there developed a red, blotchy eruption on the arms, which rapidly extended over the whole body, including trunk and lower extremities and was regarded as a generalized pellagrous eruption. In the course of a few days this rash turned brown and began to desquamate. Most of it had disappeared, leaving a healthy looking skin, within three or four weeks, but some desquamation was still present on the lower extremities at the time of death.

The confused, depressed, irritable state which was present on admission disappeared about the beginning of June, the period of delirium appearing to coincide with the acute pellagrous symptoms. After this time the patient became more cheerful, talking freely and gave a good account of her life without evidence of any mental dilapidation. There were, however, periods for two or three days at a time in which she would become depressed, entirely inaccessible, asking to be left alone, refusing food and saying she wished to die, but there was no recurrence of clouding of consciousness at these times. She explained these episodes by saying she felt so ill and wanted to go home to die.

Evidences of involvement of the *nervous system* gradually increased throughout the illness. The deep reflexes became more and more exaggerated until ankle clonus of short duration could be obtained on both sides. The Gordon paradoxical reflex appeared on both sides and finally a bilateral Babinski phenomenon. With this there was progressive weakness and wasting of muscle quite generally throughout the body.

Dizziness was a marked feature throughout the illness and she occasionally fell out of bed, apparently as the result of vertigo. In walking she was extremely unsteady and somewhat spastic, showing a constant tendency to fall towards the left.

No gross changes in skin sensibility were detected, with the exception that during the last two weeks of her life there seemed to be some blunting, but she was too ill to give much attention. At the time of the generalized eruption there was quite definitely increased tenderness of the muscles and nerve trunks which, however, disappeared in a few days.

During the last two weeks of her life there appeared *jactatoid movements* involving at first the four extremities, which became rapidly more and more violent extending even to the facial muscles, the lips, eyeballs and respiratory muscles. Accompanying this was an increasing tonic spasm of all muscles with slight retraction of the head. The jactatoid movements were sometimes so severe as to raise the patient completely off the bed. During this last two weeks she seemed to be clear, to take an interest in the presence of her daughter and son, but she often complained of an extreme dizziness and sometimes of noises in the ears like "flies." There was no vomiting at any time but the patient complained of nausea and eructations.

Blood: The blood was examined repeatedly both fresh and stained but no abnormal bodies were noted. Blood counts showed a moderate degree of secondary anemia, the red cells numbering from 4,640,000 to 4,148,000 per c.mm., the hemoglobin being estimated at 85 per cent. The white cells at the first examination numbered 16,920 per c.mm. and increased to 20,480 at the end of June. All through there was an increase of polymorphonuclear leukocytes which comprised 75 to 79 per cent. of the total. Small lymphocytes 15 to 19 per cent., large lymphocytes 2 to 5 per cent. and eosinophils 1 to 2 per cent. No abnormal white cells nor red cells were observed.

Urine: Urine examination on several occasions presented no abnormalities and the stools were searched three times, after administration of calomel and magnesium sulphate, for the presence of protozoa. Active flagellates of the type of *Trichomonas intestinalis* were present each time but no amebas were found.

Necropsy.—Death occurred at 8:30 a. m., August 17, 1911, and an *autopsy* was performed at 10:30 a. m. the same day. At the examination the body was found to be extremely emaciated. The lungs showed nothing abnormal with the exception of passive congestion and some scars of healed tuberculosis at both apices. The heart showed nothing abnormal. There was a moderate amount of sclerosis in the aorta.

The kidneys presented a slight amount of interstitial nephritis. Spleen was injected but appeared otherwise normal. The suprarenal glands showed nothing abnormal.

The gastro-intestinal tract was normal with the exception of three small ulcers in the lower part of the ileum just above the ileocecal valve. These ulcers were punched out with some heaping up at the margins but no undermining, and appeared to be healing.

The liver was engorged with blood and had a fatty appearance. Pelvic organs were normal with the exception of a submucous fibroid. The brain weighed 1,190 gm. There was microgyria of the frontal and to a less extent of the occipital lobes. The vessels showed some slight opacities and were injected. Portions of all organs were removed for examination microscopically and one-half of the brain was placed in alcohol for chemical analysis.

MICROSCOPIC EXAMINATION

Lungs: The lungs show an increase of fibrous tissue with thickening of the vessels and moderate anthracosis.

Heart. Heart muscle shows some tendency to fragmentation but no fatty change. Some cells show pigmentation about the nuclei.

Kidneys: The capsule is thickened and there is some fibrous tissue between the tubules. The vessels are all engorged and a few small hemorrhages are scattered throughout. In places the arteries show marked hyaline degeneration. The glomeruli are small, the spaces about them dilated and the capsule of Bowman thickened. Some of the glomeruli show a marked increase in connective tissue nuclei. Beneath the capsule many areas show a moderate small-celled infiltration. The epithelium of the tubules for the most part is well stained but in places that lining the convoluted tubules appears swollen and finely glandular. Many of the tubules contain a hyaline material and a few some epithelial cells.

Spleen: Capsule thickened with corresponding increase in the fibrous trabeculae. The organ is much congested and there are several hemorrhages with dark blood pigment.

Liver: The capsule is moderately thickened and there is a general increase in fibrous tissue of the portal canals. Around some of the smaller vessels in the portal canals there is also an infiltration with small round-cells. These stand out as rather widely separated islets in the section. The whole organ is markedly congested and there are a number of small hemorrhages especially beneath the capsule. The congestion of the lobules increases as the central vein is approached and here the columns of liver cells are widely separated. The liver cells stain well but there is extreme fatty degeneration of patchy distribution especially at the periphery of the lobules. Some of the cells nearer the central vein also show the fatty change, but to a less extent. The patchy distribution of this fatty change and of the small celled infiltration are striking and the same may be said of the capillary engorgement of the lobules, although this latter is more constant than the other two. The bile ducts are well stained and show no increase.

Pancreas: There is moderate increase of fibrous tissue in the pancreas and a few small hemorrhages are seen. Islands of Langerhans normal in number and appearance.

Small Intestine: Unfortunately no sections were obtained from the ulcers observed. The tissue containing them was badly fixed and could not be cut. Sections from other parts of the small intestine showed engorgement with blood and small-celled infiltration of the mucosa and submucosa in irregular patches similar to those described in Case A. D.

Thyroid Gland: This showed increased fibrous tissue with some epithelial hyperplasia; marked engorgement with blood.

Nervous System: Nerve cells; widespread chromatolysis of axonal type with marked pigmentary changes are found involving especially the larger elements. Pigmentary changes are present even in the medium sized pyramidal cells. These changes are most marked in the Rolandic regions but are present, though to a less extent, in other regions examined. Many of the cells, especially among the smaller elements also show a diffuse, dark staining which with the heaping up of satellite cells suggests the existence of a more chronic type of cell change. Similar changes are present in the Purkinje cells and the cells of the posterior root and sympathetic ganglia.

The fatty changes are very obvious in specimens stained with Scharlach both in the central system and in the sympathetic. Marchi specimens have not yet been examined.

Glia and Vessels: Contrary to the findings in the case of A. D., there is marked increase in the number of glia nuclei in all regions of the brain. In many places the satellite cells form heaps and some of the vessels are bordered by solid rows of such nuclei. Glia nuclei are present in large numbers in all layers of the brain cortex and are increased also in the white matter.

The adventitial sheaths of the arteries show multiplication of the nuclei and there is in places a proliferation of the intima. The perivascular sheaths present very slight cellular infiltration and Scharlach stains show the presence of numerous fatty granules contained within cells.

CASE 3.—Pellagra in a Woman Suffering from a Manic-Depressive Psychosis. Death One Month after Onset with Symptoms of Central Neuritis.

History.—A. S., white female, aged 36, widow. She was a native of Scotland and but little information was available concerning her previous life. She, with her husband, adopted the religion of Dowie when in Scotland and have lived in Zion City for six or seven years. They have been in fair circumstances and succeeded in purchasing a home. In 1908 when the husband was ill the patient had an attack of excitement of manic-like character lasting a few weeks. Her husband died about the end of 1908 and she apparently had an attack of depression lasting about one month, but was able to perform her housework. At the end of June, 1910, she again became restless and excited, with heightened mood. When admitted to the Elgin State Hospital July 21, 1910, she presented no evidences of somatic disease but was exalted. Her thoughts and acts were strongly colored by her religious views, with some self-appreciation and she was somewhat restless. In October she became more excited, singing and dancing, interfering with others, in all this giving explanations on the basis of her religious exaltation.

A pellagrous eruption with emaciation and diarrhea were noted in May, 1911, and she died June 20, 1911, after a period in which muscular rigidity with jactatoid movements with diarrhea were noted.

The autopsy was performed by Dr. H. Smith about 24 hours after death. Unfortunately no record of the gross findings is available.

MICROSCOPIC EXAMINATION

Liver: The liver shows no definite increase of fibrous tissue either in the capsule or interlobular septa. The vessels and intralobular capillaries are engorged, the latter especially in the region of the central veins. Numerous small extravasations of blood are present within the lobules. Marked fatty degeneration of the liver cells at the periphery of the lobules is present and there are many islets of infiltration with small round-cells of low grade of intensity in the interlobular septa.

Kidneys: The capsules are thickened and fibrous tissue is increased around the vessels, between the lobules and in Bowman's capsules. The vessels are engorged and there are small hemorrhages scattered throughout, but especially in the medullary rays. The glomeruli are well stained with some increase of connective tissue nuclei and are surrounded by a widened space. The secreting tubules show some swelling of cells with diffuse-staining and indistinctness of outline while many contain an albuminoid material.

Heart: The heart muscle shows thickening of vessel walls with pigmentary changes in the muscle cells.

Spleen: The spleen presents moderate thickening of capsule and trabeculae with here and there small hemorrhages.

Lungs: The lungs show many alveoli filled with a homogeneous material staining very faintly with eosin which sometimes contains no cellular elements but frequently numerous red blood-cells and here and there shed epithelium. There is no leukocytic infiltration to suggest pneumonia.

Suprarenals: In the suprarenal glands the vessels of the inner layers of the cortex and of the medulla are extremely engorged with blood. The parenchyma is much degenerated and in many places the cells do not stain at all, being represented only by a granular detritus.

Nervous System: The nervous system in this case has not yet been worked up. Sections from the cortex stain badly with the Nissl stains showing but little differentiation of the granules. Nevertheless many of the larger pyramidal cells show swelling with diffuse coloration of the nucleus which is irregular in outline

and displaced to the periphery of the cell. These changes are also very marked in the cells of the dentate nucleus of the cerebellum. Pigmentary changes have not been observed in anything like the same degree seen in the other cases. There is a moderate increase of glia nuclei along the walls of the vessels but not elsewhere. The vessel walls show moderate increase of adventitial nuclei but no perivascular infiltration.

CASE 4.—Pellagra in a Man with Advanced Arteriosclerotic Changes and Dementia. Death Six Weeks after Onset with Central Neuritis.

History.—F. M., white male, blacksmith, said to have been insane since 1901 and to have had a previous attack in 1886. He was admitted to the Elgin State Hospital in 1904 at the age of 67. He then showed some loss of memory and derogatory delusions. He was depressed and cried easily, refused food and threatened suicide. His physical health was poor and he suffered from hemorrhoids. He gradually failed in strength.

Pellagrous eruption with diarrhea developed in June, 1911, which improved in July, but he became worse again July 10 and died July 16 without further acute symptoms of pellagra, but with signs of central neuritis.

Necropsy.—At the necropsy the pellagrous pigmentation was still present and the body was much emaciated. The brain showed some atrophy of the cortex and atheroma of vessels. The lungs showed hypostatic congestion and healed tuberculosis at the right apex. The coronary vessels were sclerotic but there were no other cardiac changes. The spleen and kidneys were reported to present no changes. The liver was firmer than normal. In the large intestine were a number of circular ulcers chiefly in the transverse and descending colon. They were from $\frac{1}{8}$ to $\frac{1}{2}$ inch in diameter.

MICROSCOPIC EXAMINATION

Microscopically the principle changes are: Marked engorgement of the vessels of the *liver* with moderate fatty degeneration of the cells at the periphery of the lobules. The connective tissue is but little if at all increased. Small hemorrhages are present in places. The *kidneys* show chronic interstitial nephritis with the formation of small sub-capsular cysts. Small extravasations of blood are present, especially beneath the capsule. The tubules stain poorly and many contain an albuminoid material and in places epithelial cells. The pyramids are markedly congested and many vessels show hyaline change, some being occluded. The *spleen* shows some increase of fibrous tissue and there are small scattered hemorrhagic areas. The arteries show some hyaline change of the intima. The *intestinal ulcers* extend down to the submucosa and show a moderately acute small-celled infiltration. No amebas were found. Areas of infiltration with small round-cells are also present apart from the ulcers and extend even into the muscularis.

Nervous System: In this case the picture is complicated by the marked changes which are present in the vessel walls. A small hemorrhage about 3 mm. in diameter was found in the crista of the pons and another microscopical in size in the anterior cornua in the cervical region. Both were recent and in the latter the nerve cells lying in the midst of the extravasated blood cells still stained well showing well-marked Nissl granules, so that it seemed probable the extravasations were due to post-mortem injury.

Chromatolysis is well marked in the giant pyramidal cells of the precentral region and also in the larger pyramidal cells elsewhere. The Purkinje cells in the cerebellum stain faintly and some show central chromatolysis with displacement of the nucleus. Similar changes are found in a few cells in the anterior horn of the cord and more extensively in the cells of Clarke's column.

Pigmentary changes of a fatty nature are widespread throughout the nervous system as shown by Scharlach staining and this involves not only those cells

showing chromatolysis but also the smaller and other cells showing good Nissl staining. Similar fatty granules are present in large numbers contained within cells lying in the sheaths of the vessels.

The blood-vessels show marked hyaline changes in the intima, many of the smaller vessels appearing to be almost occluded. There is also hyperplasia of the adventitial coats but no small-celled infiltration of the perivascular sheaths. The glia nuclei are moderately increased both along the vessels and surrounding the nerve cells.

CASE 5.—Prolonged Attack of Pellagra with Acute Exacerbations in a Man Suffering from Chronic Alcoholism with Marked Dilapidation. Death Six Months after Onset.

History.—E. J., white male, upholsterer, 41 years of age at time of death. He was a native of Sweden and had a brother and a sister who were feeble-minded. He was a heavy drinker and was irritable and unstable. In January, 1901, at the age of 31 he was arrested for drunkenness but continued in an excited state, preaching and expressing ideas of persecution. When admitted to the Elgin State Hospital in January, 1901, he was very restless and excited but seemed in good health. He continued to be violent and quarrelsome for about six weeks and then became quieter, although still quarrelsome at intervals all through his stay in the hospital. In 1908 he had an attack of acute rheumatism and is noted at that time as being "considerably demented."

Examination.—Pellagrous erythema on the hands was noted in May, 1911, and reported as "very fiery" on July 31, 1911. At this time he was also emaciated and much weaker but without any acute mental symptoms. The pellagrous eruption was still acute on August 15 and he also had stomatitis, salivation and diarrhea. August 31 the stools were examined for amebas with negative results and the blood is reported as showing a high color index. Diarrhea continued, with progressive exhaustion and emaciation until death October 29, at which time the eruption was still present but of purple color, with marked desquamation. Plantar reflexes were of flexor type every day for two weeks before death.

Necropsy.—The necropsy was performed by Dr. Wittman on October 29. The body was much emaciated and the muscles generally thin and atrophic. The heart was extremely flabby but no other abnormalities were noted in it nor in the lungs. The liver was described as dark brown with very obscure markings. The kidneys showed some evidences of interstitial nephritis but no other findings of importance were detected. The intestines showed no ulceration.

Microscopically the only findings of importance were as follows: The *liver* showed moderate fatty degeneration following the outline of the lobules and there were small islets of infiltration with round-cells in widely separated areas of the portal connective tissue. The capillaries were engorged especially near the central veins. The fibrous tissue was not definitely increased.

The nervous system in this case has not yet been examined.

(To be continued.)

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EXPERIMENTAL NOTES ON THE INFLUENCE OF THE ADRENALS OVER THE PANCREAS *

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PHILADELPHIA

In a series of previous contributions, we have dealt at some length with certain relations between the pancreas and other organs of the body, particularly the ductless glands. Our experimental work covered a period of about five years, and it may be well, better to understand our present remarks, to repeat the main conclusions reached. For our present purposes they are as follows:

1. The flow of juice from the pancreas, whether excited by secretin injected intravenously, by HCl placed in the duodenum, or by normal chyme, may be inhibited by the intravenous injection of extracts of the pituitary or adrenal glands.

2. This inhibition may last some time after the body as a whole seems to have recovered from the rise in blood-pressure and is independent of systemic blood-pressure. The exact *modus operandi* is not clear.

3. Removal of the adrenal glands from otherwise normal dogs under circumstances which allow of observation of the flow of pancreatic juice, induces sooner or later a flow from the pancreas which persists until death, and sometimes lasts for hours.

4. This flow has been equalled in duration and activity by only the processes, natural or experimental, which depend on activation by duodenal secretin.

5. It may occur with a fairly high systemic blood-pressure though it generally occurs when the systemic blood-pressure is low.

In process of extending our observations and of attempting a solution of some of the many related problems, we came across some phenomena which in a rather striking way tend to corroborate our earlier work and also present some points of interest themselves. We are reporting them now, in brief form, because of interruptions which delayed further consecutive work.

Having established to our satisfaction that the removal of the adrenals from dogs induces a flow from the pancreas, it remained to be seen what the effect might be on such a flow of the agents which influence that caused by secretin.

* Read before the American Society for the Advancement of Clinical Investigation. Atlantic City, New Jersey, May 13, 1912.

*Manuscript submitted for publication April 19, 1912.

If the flow from the pancreas is induced by the removal of an influence which the adrenals normally exert over that gland, the flow should cease when that influence is restored.

We tried to adduce evidence on this latter point by direct examination of the blood for epinephrin by means of the Meltzer-Ehrmann frog-eye test, by transfusion of the hind legs of the frog (Trendelenburg), and by the use of the unstriped muscle of the intestine (Cannon), but without satisfaction from any of these methods.

This failure we do not mean to limit to the examination of the serum of animals deprived of their adrenals; we have not been able, in many attempts, to obtain satisfactory results with any method for the quantitative determination of epinephrin in dogs' serum.

The frog-eye test of Ehrmann and Meltzer, the transfusion test of Trendelenburg, the colorimetric methods, such as that of Comesatti, the intestinal strip of Cannon, all work well when epinephrin is being tested in dilution, in sodium chlorid or in Ringer's solution. But when the serum of the dog is being studied the results of control experiments seem to become irregular and unreliable.

EXPERIMENTS

We experimented, then, with a series of seventeen dogs as follows:

The animals were all fasted for 36 hours prior to operation to avoid complicating results from digestive activities, and after anesthetization with ether, the adrenals were removed through the abdomen and a graduated glass cannula was inserted into the pancreatic duct according to the technic described in our earlier articles.¹

The abdominal wound was then closed, a cannula introduced into the trachea to register respiration, and connection established between the carotid artery and a mercury manometer.

The respiration and blood-pressure were then respectively registered by ink pens at different levels on a kymographion drum supplied with an "endless" roll of paper.

The time was marked in seconds on a base line and the flow of pancreatic juice, when it occurred, by noting its passage past divisions on the pancreatic cannula, and by electrically registering the same by interruptions in another base line.

After establishing the above, there ensued a wait of some hours pending a flow of pancreatic juice; after a variable period this took place, usually with increasing rapidity, until, rarely, its registration became difficult.

1. Sweet, J. E., and Pemberton, Ralph: Experimental Observations on Secretin, with Especial Reference to Diabetes and Malnutrition. *THE ARCHIVES INT. MED.*, February, 1908.

Pemberton, Ralph, and Sweet, J. E.: The Inhibition of Pancreatic Activity by Extracts of Supra-renal and Pituitary Bodies. *THE ARCHIVES INT. MED.*, July, 1908.

Pemberton, Ralph, and Sweet, J. E.: Further Studies on the Influence of the Ductless Glands on the Pancreas. *THE ARCHIVES INT. MED.*, May, 1910.

Sweet, J. E., and Pemberton, Ralph: The Induction of Pancreatic Activity by the Removal of the Adrenals. *THE ARCHIVES INT. MED.*, November and December, 1910.

Coincidentally there would exist a lowering of the blood-pressure, which was usually somewhat disturbed by the initial operation, but then returned to a fairly constant level, slightly lower than before operation. From here there would shortly ensue, imperceptibly at first, a steady decline of its height until death. We have discussed this in greater detail elsewhere.¹

Some period was then selected when the pancreatic flow seemed definitely established and an intravenous injection was given of some commercial form of epinephrin.

Coincident with the initial rise of blood-pressure would appear a marked slowing, and, after a few seconds, an apparent cessation, of the pancreatic flow. With or shortly after the return of the blood-pressure to nearly or quite its former level, the pancreatic flow would again appear, at first slowly and then faster until the former rate became equaled or surpassed.

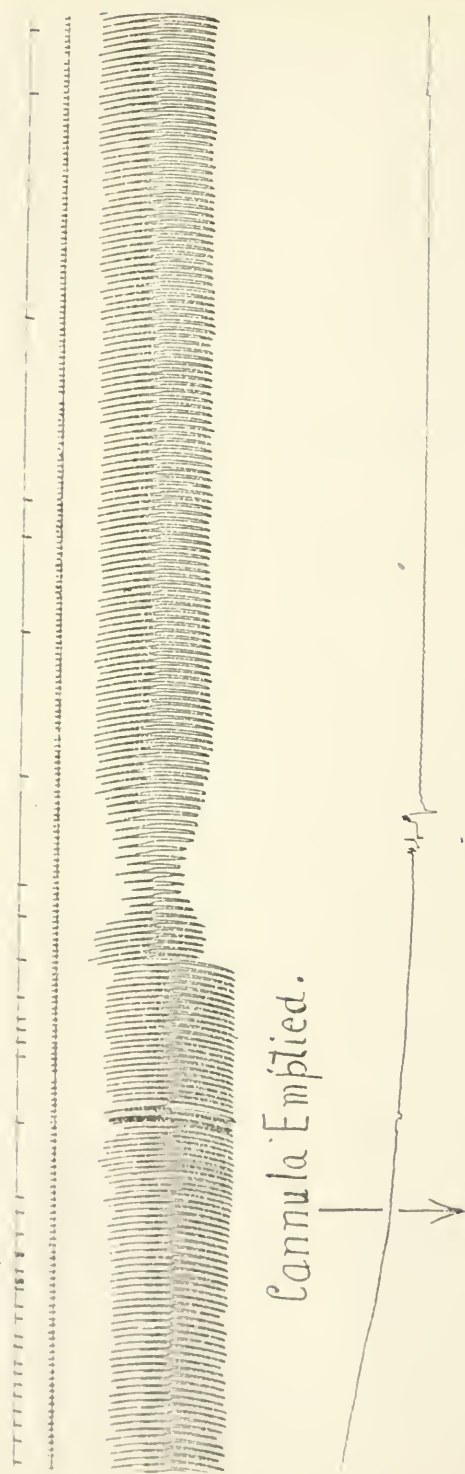
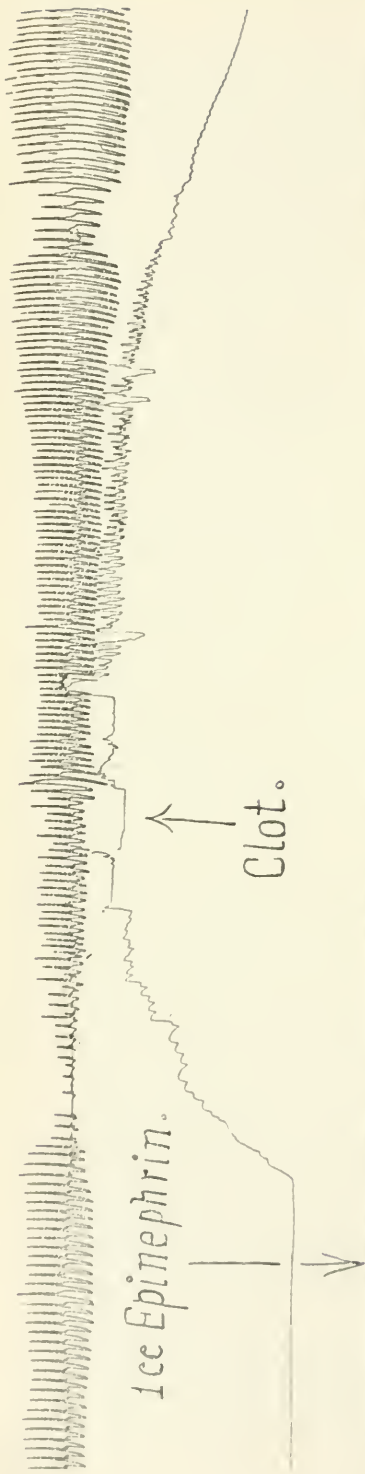
A repetition of the injection of epinephrin would produce identical results, the flow of pancreatic juice ceasing and returning each time. This could be repeated almost indefinitely and in some of our animals was obtained nine consecutive times, the animal in such case being then deliberately killed.

We have in this flow a partial analogue to the condition which sometimes takes place just before death in a normal dog, whose pancreatic flow is similarly watched. In such a dog, there not infrequently occurs what we have elsewhere recorded as a terminal flow, consisting of one or two cannulas (1 to 2 c.c.) of juice. We have previously called attention to the points of similarity between the normal dog after a period of ten to fifteen hours' consecutive etherization, and the dog without adrenals after a period of only three or four hours of anesthesia. The asthenic state, low blood-pressure and tendency to a pancreatic flow in the former are possibly expressions of the same want of suprarenal secretion which possibly exists in the latter.

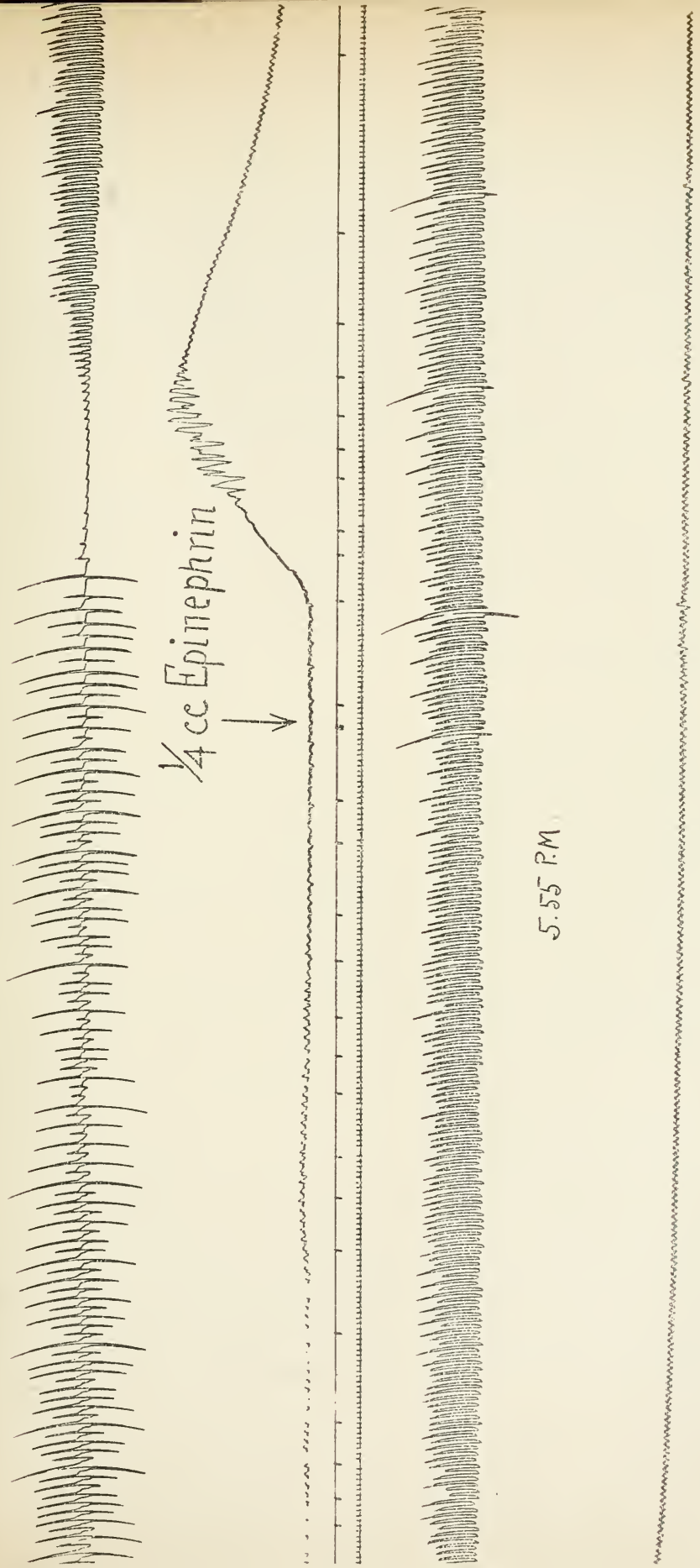
The entire consonance of the inhibition of pancreatic flow with the injections of adrenalin and rise of blood-pressure on the one hand and the return of the pancreatic flow with a fall of blood-pressure on the other, is strikingly significant. And if it be borne in mind that the pancreatic flow exists apparently only because of the ablation of the adrenals, there seems to be found a strong argument for correlation of action between the two glands.

It does not follow of course that the rise and fall of blood-pressure occurring after the injection of epinephrin are in themselves causative, respectively, of the inhibition and return of pancreatic flow. They tend only to corroborate the belief that the amount of available epinephrin is then diminished or absent; and the action of the injected epinephrin on the pancreas may be by means other than vasoconstrictor, as some of the evidence indicates.

Summing up the situation, then, it seems possible that the flow of pancreatic juice which follows the removal of the adrenals, occurs coincidentally with a diminution or absence of the blood-pressure-raising or other principle of these glands.



Record 1.—(From Experiment 8.) The section shown was preceded by four injections and followed by one injection (six in all), giving similar results. It shows the flow produced by removing the adrenals, the inhibition of this flow by 1 c.c. epinephrin and the return and persistence of the flow when the effect of the epinephrin wears off. (This dog received earlier a transfusion of normal dog's blood, but Record 2 and other Experiments, show that the end result was not thereby affected).



Record 2.—(From Experiment 14.) The section shown was preceded and followed by four injections (nine in all) giving similar results. It shows the flow produced by removing the adrenals, the inhibition of this flow by .25 c.c. epinephrin and the return and persistence of the flow when the effect of the epinephrin wears off.

There seems, furthermore, to exist under these circumstances such a determined and definite flow of pancreatic juice, that repeated injection of epinephrin is not sufficient to stop it permanently.

One fact which militates against this as a function of normal physiology, is that the flow sometimes occurs late in the life of the animal, and in some experiments the flow seems to usher in the end. In such cases the animals can be kept alive, however, for long periods, during which pancreatic flow tends to occur, by repeated injections of epinephrin: after each of which the blood-pressure, previously at a moribund level, is raised to a height compatible with life.

It may be argued that the conditions of such a flow are beyond the pale of normal physiological activity, but it must be borne in mind that the flow begins mildly and often or generally when the animal is apparently in excellent condition. Therefore, while we do not assert that the adrenals thus control the pancreas under the usual conditions of life, such a possibility cannot be overlooked, much less denied in view of this demonstrable, experimental influence.

CONCLUSIONS

(On the basis of our previous work)

Intravenous injections of epinephrin inhibit the flow of pancreatic juice, whether this be caused by hydrochloric acid, normal chyme or secretin.

This inhibition may last some time after the blood-pressure has apparently returned to normal, and is independent of the systemic blood-pressure.

Removal of the adrenal glands from dogs otherwise normal induces a flow of pancreatic juice which may last for hours.

It may occur with a fairly high systemic blood-pressure, though it generally occurs when the blood-pressure is low.

(On the basis of the work now reported)

1. Injections of epinephrin made when the flow, following removal of the adrenals, is at its height, inhibit the flow.

2. Shortly after or before the blood-pressure falls to its previous level, the pancreatic flow returns. It can thus be repeatedly inhibited and it then repeatedly returns. The tendency to flow seems very strong.

3. Since removing the adrenals induces a flow and since injections of epinephrin then inhibit the flow; and since the flow returns when the effect of the injection wears off (which last can be repeatedly demonstrated in one animal), it is difficult to escape the thought that there is normally some such relation between these glands.

SYNOPSIS OF EXPERIMENTS

Experiment 1.—Jan. 10, 1911. Both adrenals out; blood-pressure gets low, two hours later 2 c.c. old epinephrin² raises it; better condition; 1.5 c.c. epinephrin given; 2 c.c. epinephrin; moribund; no result 12.45 p. m. no flow.

Experiment 2.—Jan. 10, 1911. Adrenals out; no flow; early death; no result.

Experiment 3.—Jan. 11, 1911. No. 1. Both adrenals out; early death; no evident cause; spleen very large.

Experiment 4.—Jan. 11, 1911. No. 2. Both adrenals out; no result; early death.

Experiment 5.—Jan. 12, 1911. Adrenals out; adrenals not broken or squeezed. No flow for a long time at start; flow; 0.5 c.c. epinephrin gives inhibition; return of flow and blood-pressure. Dog gets low with flow (terminal); 1 c.c. epinephrin raises blood-pressure (which falls fairly soon). Flow inhibits but does not return well again.

Experiment 6.—Jan. 28, 1911. Both adrenals out by 9:47; removed easily. About 2:15 good flow. Later 0.25 c.c. epinephrin inhibits; blood-pressure falls soon; no return for ten minutes; then good flow. 0.166 c.c. epinephrin inhibits; clot; flow soon returns; 1 c.c. of 1/1,000,000 inhibits, and clots cannula; no rise in blood-pressure; return of flow and death.

Experiment 7.—Jan. 30, 1911. Adrenals out; flow good; 0.1 c.c. epinephrin inhibits; blood-pressure falls rather slowly and flow returns well; 1 c.c. epinephrin inhibits and flow returns after a rather slow fall; good flow again inhibited by 0.25 c.c. epinephrin and dog dies.

Experiment 8.—Feb. 1, 1911. Both adrenals out at 10:13; flow at 4 p. m.; transfusion of dog's blood raises blood-pressure; slightly slows flow; flow returns; transfusion then does not raise blood-pressure much and flow continues; very good flow follows; 0.1 c.c. epinephrin raises blood-pressure moderately. Flow continues unabated. Blood-pressure falls rather soon; 0.2 c.c. epinephrin raises blood-pressure more; falls rather soon; flow slowed; returns well; 0.25 c.c. epinephrin affects blood-pressure same way and slows flow; returns; 0.5 c.c. epinephrin raises blood-pressure well; rather quick fall; distinct inhibition; good return; 1 c.c. epinephrin keeps blood-pressure up fairly well 3½ minutes; marked inhibition; good return; 1 c.c. epinephrin; sharp rise; clot; inhibition; good return of flow; 4 c.c. epinephrin keeps blood-pressure up 10 minutes; strong inhibition; good return; dog being kept alive by epinephrin; now allowed to die, 6:10 p. m.; intestine and stomach empty.

Experiment 9.—Feb. 3, 1911. Both adrenals out. Flow not affected by transfusion. (One adrenal broke in a. m.) No definite conclusion to be noted.

Experiment 10.—Feb. 7, 1911. Both adrenals out at 10:32 a. m. Not torn; flow; transfusion of dog's blood; rise in blood-pressure; some inhibition; returns; then good flow. (Not much blood transfused.)

Experiment 11.—Feb. 8, 1911. Adrenals taken out. No result.

Experiment 12.—Feb. 9, 1911. Both adrenals out; right adrenal torn; flow good; in three hours dog gets low; 1 c.c. epinephrin revives; blood-pressure falls fast; flow soon again; transfusion; slight rise; no apparent inhibition; 0.75 c.c. epinephrin inhibits; slight return of flow as dog dies after four hours.

Experiment 13.—Feb. 14, 1911. Both adrenals out; right adrenal badly torn; slight flow—not recorded. Transfusion seems to start slight flow; stops; transfusion seems to start it more actively again. Later a flow; 0.166 c.c. epinephrin inhibits with a very slight rise; flow returns; cannula comes out; 0.5 c.c. epinephrin gives sharp rise and quick fall. Killed.

2. The epinephrin used in these experiments was the adrenalin of Parke, Davis & Co.

Experiment 14.—Feb. 17, 1911. Both adrenals out at 11:08 a. m. Neither injured. Rather poor flow; inhibition by epinephrin; flow returns: at 5:20 good flow (cannula leaking before); 0.25 c.c. epinephrin inhibits: moderate slow fall of blood-pressure and return of flow: *dog low*; 0.25 c.c. epinephrin inhibits: quicker drop: flow returns soon; 0.25 c.c. epinephrin; quick fall: inhibition; return of flow; 0.25 c.c. epinephrin: inhibition; return of flow; dog dying: 0.25 c.c. epinephrin; inhibition; return of flow: 0.25 c.c. epinephrin; good rise; inhibition: return: 0.25 c.c. epinephrin; clot: inhibition: return of flow; 0.75 c.c. epinephrin: big rise; quick drop; return of flow: dog allowed to die. 6:30 p. m.

Experiment 15.—March 9, 1911. Adrenals out (right torn). No flow. *Secretin* given. Flow from it. Then later a spontaneous flow which lasts some time and then subsides; starts again toward end and gives several cannulas full. No epinephrin given.

Experiment 16.—March 10, 1911. Both adrenals out; neither torn: blood taken late for frog-eye test. Flow. Medulla inhibits and raises blood-pressure. Flow returns slightly. When dog is moribund 0.5 c.c. epinephrin and artificial respiration bring back life and also flow later; moribund again: 10 c.c. cortex fails to work; 0.5 c.c. epinephrin causes return of life and blood-pressure which falls quickly. (Given twice quickly): no real flow again. (The specimens of suprarenal cortex and medulla were supplied by Parke, Davis & Co. in the form of powder.)

Experiment 17.—March 9, 1911. Fed dog: normal pancreatic flow; under ether: pancreas congested; lacteals white; flow later; hemorrhage into pancreatic duct, vitiates experiment. Killed.

Experiment 18.—March 11, 1911. No result.

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THE ABSORPTION OF FOOD IN TYPHOID FEVER *

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Since von Hösslin and the Russian investigators made their studies on the assimilation of foods in fever twenty to thirty years ago, very little work has been done on the subject. In the meantime, the methods of analysis have been improved and the diet in typhoid has in some clinics been increased so much that patients in the height of their fever are given more food than was formerly given in the second week of convalescence. The question naturally arises as to whether the patients are absorbing the food or are passing it undigested through the intestines.

At the suggestion of Dr. Warren Coleman who has for five years been using a very liberal diet in his service at Bellevue Hospital, I undertook a study of the question in his wards. Six patients with typhoid were studied over periods lasting from five to twenty-one days. They were fed the so-called "high calory diet," which consists of about 1,000 c.c. milk, 300-400 c.c. 20 per cent. cream, 100-200 gm. lactose, two or three eggs, a couple of slices of toast and some butter. This furnishes between two and three thousand calories and one or two thousand calories more can be added in the form of larger amounts of the above or in the form of boiled rice, oatmeal, mashed potato, cream of wheat, apple sauce, custard or ice cream. This diet has been fully described by Shaffer¹ and Coleman,² and is the only recorded diet which has succeeded in maintaining the patients in nitrogen and weight equilibrium. Clinical experience has shown that patients do well on this diet and it was no surprise to find that they could absorb the enormous amounts of food almost as well as normal individuals.

*From the department of applied pharmacology and the second medical division of Bellevue Hospital, New York. All analyses were made in the laboratory of the department of physiology. I am indebted to Professor Graham Lusk for the privilege of working in his laboratory and for many valuable suggestions during the course of the work; also to Dr. Coleman and Dr. Dana for permission to use patients, in their wards, and to Mr. Rudolph H. Harries and Mr. John M. Janson for their assistance in making many of the analyses.

*Manuscript submitted for publication April 13, 1912.

1. Shaffer and Coleman: Protein Metabolism in Typhoid Fever. *THE ARCHIVES INT. MED.*, 1909, iv, 538.

2. Coleman: The High Calory Diet in Typhoid Fever: A Study of One Hundred and Eleven Cases. *Am. Jour. Med. Sc.*, 1912, cxliii, 77.

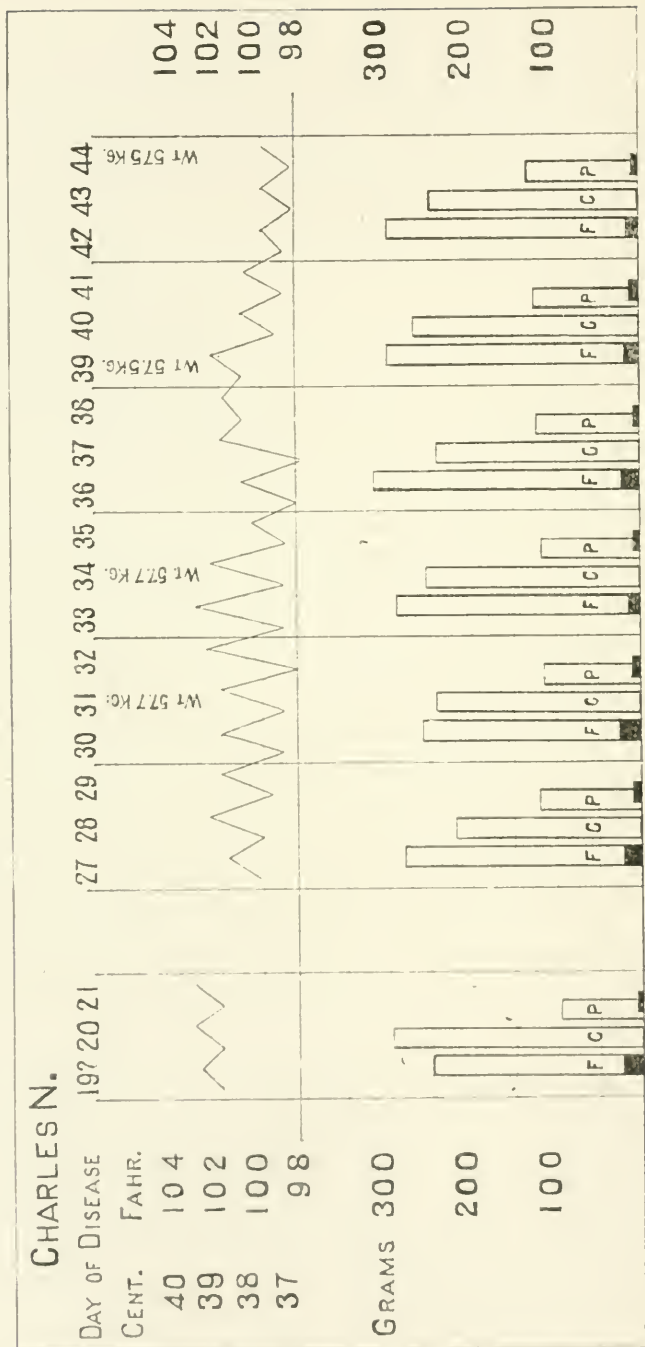


Chart 1.—Temperature curves in Case 1, Charles N. The column shows the average daily weight of fat, carbohydrates and protein in food; the solid bases show amounts absorbed.

NORMAL ABSORPTION

In the case of normal individuals who are given an easily-digested diet, the food is practically all absorbed and the feces consist almost entirely of bacteria and the secretions of the intestinal tract.^{3, 4} The feces of a starving person can contain from 0.1 to 0.3 gm. of nitrogen a day, and of a person on a nitrogen free diet as much as 0.5 to 0.87 gm. of nitrogen. Reducing bodies and ether-soluble substances are also present in the stools when none is given in the food. In addition to these secretions of the intestinal tract, however, considerable amounts of food

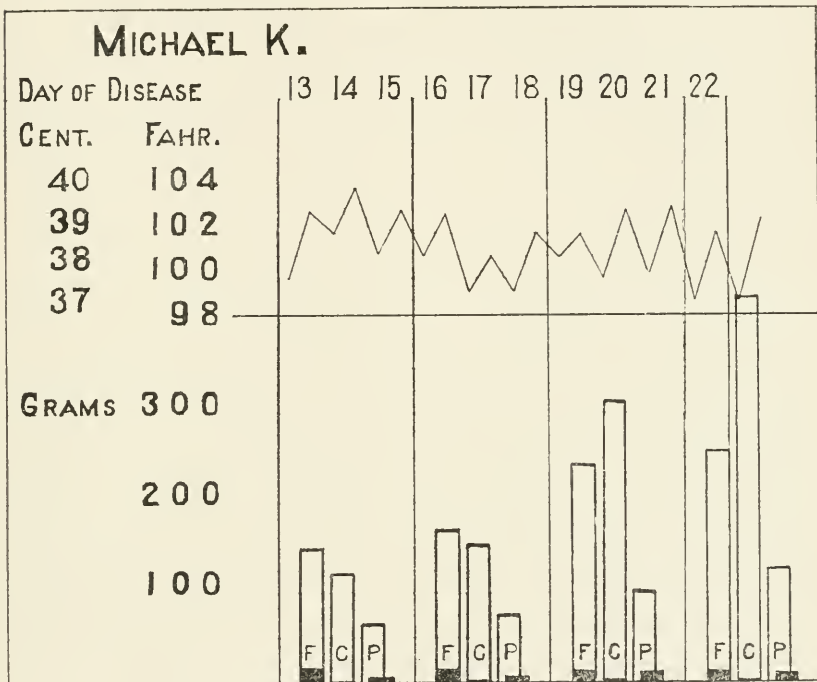


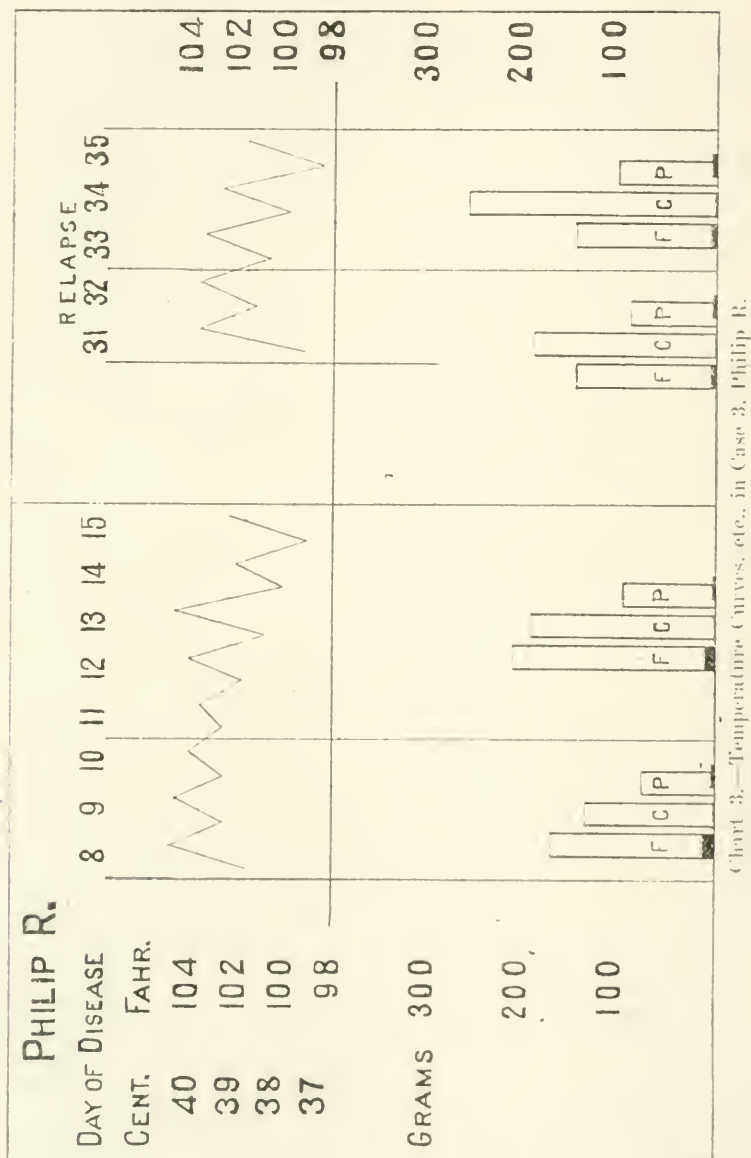
Chart 2.—Temperature curves, etc., in Case 2, Michael K.

residue do appear in normal persons who are given coarse or poorly-cooked food, or food in unusually large quantities. As a rule, sugars are completely absorbed, and well-cooked starches almost completely. Emulsified fats of low-melting point are better absorbed than fats of high-melting point. When fats are given in amounts greater than 350 gm. the intestine does not absorb well. (It may be noted that one of the typhoid patients in this series was given 327 gm. of fat on one day.) In

3. Lusk: The Science of Nutrition. Philadelphia, 1909, p. 45.

4. Mendel and Fine: Studies in Nutrition, Jour. Biol. Chem., 1912, xi, 5.

considering the absorption of any particular food, such as fat for instance, one can get a false idea if one considers the percentage loss alone without



considering both the grams of fat in the food and in the feces. This is shown in a series of experiments by von Noorden⁵ on the same individual.

5. Von Noorden: *Lehrb. der Path. des Stoffwechs.*, Berlin, 1893, p. 33.

4.2 gm. fat in food — 51.1 per cent. loss in feces.

42.2 gm. fat in food — 10.9 per cent. loss in feces.

80.2 gm. fat in food — 6.36 per cent. loss in feces.

It is hard to state the normal percentage of loss of the various food-stuffs. Rubner⁶ gives the accompanying table (Table 1) of the averages of many of his experiments.

TABLE 1.—FOOD ABSORPTION: NORMAL INDIVIDUALS

Food	Percentage Loss		
	Fat	Carbo-hydr'te	Protein
Roast beef	2.6
Hard boiled eggs	4.4	...	2.6
Milk	5.2	0	7.1
Fine white bread	1.1	21.8
Rice	0.9	20.4
Potato	0.7	19.5
Mixed diet with >			
Bacon (99 gm. fat)	17.4	1.6	12.1
Bacon (195 gm. fat)	7.8	6.2	14.0
Butter (214 gm. fat)	2.7	6.2	11.3
Butter and bacon (350 gm. fat)	12.7	6.8	9.2

In certain pathological conditions the absorption of food can be greatly interfered with. Obstruction to the flow of pancreatic juice or bile can diminish the absorption of fats greatly. In certain cases of intestinal indigestion carbohydrates are poorly absorbed. Tuberculosis or cancer of the intestine or any very severe diarrhea can increase greatly the nitrogen content of the feces. A moderate diarrhea has but little effect on absorption.

PREVIOUS STUDIES OF ABSORPTION IN TYPHOID

Von Hösslin,⁷ in 1882, studied most carefully a series of typhoid patients fed on various diets, such as ham or milk or eggs, or the juice of pressed meat. The total calories of his diets were not high and most of his patients suffered from diarrhea. The nitrogen of the food varied between 10 and 21 gm. and the feces nitrogen from 0.9 to 2.2 gm. or from 7.6 to 13 per cent. of the nitrogen ingested. With 50 to 135 gm. of fat in the food the feces contained from 5 to 10 gm. or from 6 to 10 per cent. The carbohydrates of the feces were not determined directly. Some of his patients were put on very low diets containing 1 to 3 gm. fat, 8 to 11 gm. carbohydrate and no protein. During these periods of practical

6. Rubner, Gruber and Ficker: *Handb. der Hygiene*. Leipzig, 1911. i. 131.

7. Von Hösslin: *Virchows Arch. f. path. Anat.*, 1882, lxxxix. 95.

starvation, the feces contained 0.8 to 5 gm. of ether extract a day and from 0.4 to 0.8 gm. of nitrogen. Von Hösslin came to the conclusion that foods were absorbed almost as well in typhoid fever as in health.

Shortly after his work was published the Russians of Chudnowsky's clinic, where typhoid patients were given liberal diets, began a series of investigations on the same subject. Most of their work is published in Russian and has never received the attention it deserves.⁸ Their work on the whole supports von Hösslin's contentions. They found the assimilation of protein to be almost as good as in health, and they found that cold baths, antipyretics, the drinking of water in large amounts and of alcohol in small amounts seemed to increase the percentage of protein absorbed. Large enemas of hot water seemed to decrease the absorption. Aikinov,⁸ who included in his dietary 20 gm. of blackberries, found from 4 to 6 gm. of nitrogen a day in the feces of his patients. Gruzdiev,⁸ when he gave a very liberal diet of milk and bread with 30 to 45 gm. of nitrogen, found 4 to 11 gm. of nitrogen in the feces. The other observers using moderate and easily-digested diets obtained only 1 to 3 gm. per day. Chernoff,⁸ drawing his conclusions from a small majority of his

8. Copies of the inaugural dissertations are deposited in the Library of the Surgeon General's Office, Army Medical Museum, Washington. Files of Vrach are kept at the Academy of Medicine, New York and probably at most of the other large medical libraries. Abstracts giving some of the tables can be found in Atwater and Langworthy: *Digest of Metabolism Experiments*, U. S. Dept. of Agri., Bull. No. 45, 1897, p. 181.

It must be remembered that transliterations of the same Russian name may differ greatly.

Chernoff (Tschernoff): *Fat Absorption of Adults and Children with and without Fever*. Inaug. Diss. (Russian), St. Petersburg, 1883.

Kurkutoff, A. G. (Kurkutow): *On the Question of the Influence of Fever and Antipyretic Measures on the Assimilation of Fat by Typhoid Patients*. Inaug. Diss. (Russian), St. Petersburg, 1891.

Sassetzky (Zasietski): *Influence of Fever and Antipyretics on the Metabolism and Assimilation of the Proteins of Milk (Typhus fever studied)*. Inaug. Diss. (Russian), St. Petersburg, 1883; also *Virchow's Arch. f. path. Anat.*, 1883, xciv, 533.

Khadgi (Chadchi): *The Qualitative and Quantitative Assimilation and Metabolism of Nitrogen in Typhoid Fever*. Inaug. Diss. (Russian), St. Petersburg, 1886 (abstracted by Puritz). See following paragraph.

Puritz: *Reichliche Ernährung bei Abdominaltyphus*. *Virchow's Arch. f. path. Anat.*, 1893, cxxxi, 327. Also Inaug. diss. (Russian), St. Petersburg.

Matzkevich: *The Influence of Copious Water Drinking on the Assimilation and Metabolism of Nitrogen in Typhoid Fever*. Inaug. diss. (Russian), St. Petersburg, 1890.

Gruzdiev: (Same subject) *Vrach*, 1890, xi, 213.

Gesler: *Influence of Enemas on Assimilation and Metabolism of Nitrogen in Typhoid*, *Vrach*, 1890, xi, 479.

Aikinov: *On Feeding Patients with Alkaline Albuminates of Eggs*. Inaug. Diss. (Russian), St. Petersburg, 1889.

Diakonov: *Influence of Alcohol Upon Assimilation and Metabolism of Nitrogen in Typhoid Fever*. Inaug. Diss. (Russian), St. Petersburg, 1890.

cases, states that the assimilation of fat is better during the height of typhoid fever than during convalescence or health. Kurkutoff,⁸ on the other hand, found that the absorption of fat was poorer during fever and varied with the gravity of the disease.

On reviewing the figures of all these Russian investigators, one receives the impression that the absorption of food depends chiefly on the patient's general condition, and as this is improved either by the natural course of recovery or by therapeutic measures, the absorption of food

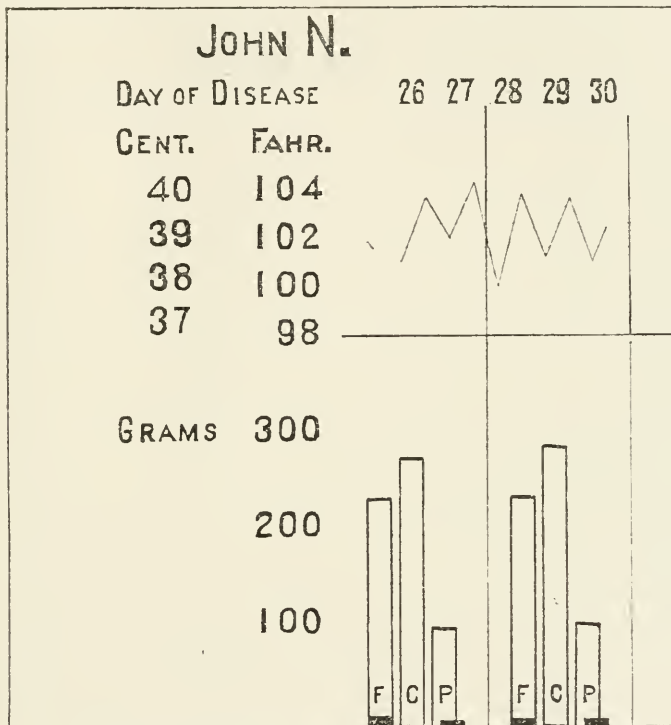


Chart 4.—Temperature curves, etc., in Case 4, John N.

improves also. It may be noted in passing that the Russians, even when using liberal diets with very large amounts of protein, were unable to keep their fever patients in nitrogen equilibrium.

Von Leyden and Klemperer⁹ were the next to study the absorption of foods incidental to their unsuccessful attempt to establish nitrogen equilibrium in typhoid. They found that patients with high fever when given 100 gm. of easily-digested fat lost from 6 to 11 per cent. in the

9. Von Leyden and Klemperer: Von Leyden's Handb. der Ernährungstherapie, 1904, ii, 332.

feces, and lost about 9 per cent. of an equal amount of protein. Carbohydrates appeared in the feces only when very large amounts were given in the food or when the patients suffered from profuse diarrhea.

CASES STUDIED

The six typhoid cases on whom the present work was done were unselected cases from the wards of the second medical division (Cornell Division) of Bellevue. It so happened that none of the patients had diarrhea during the period of investigation, but one is struck by the fact

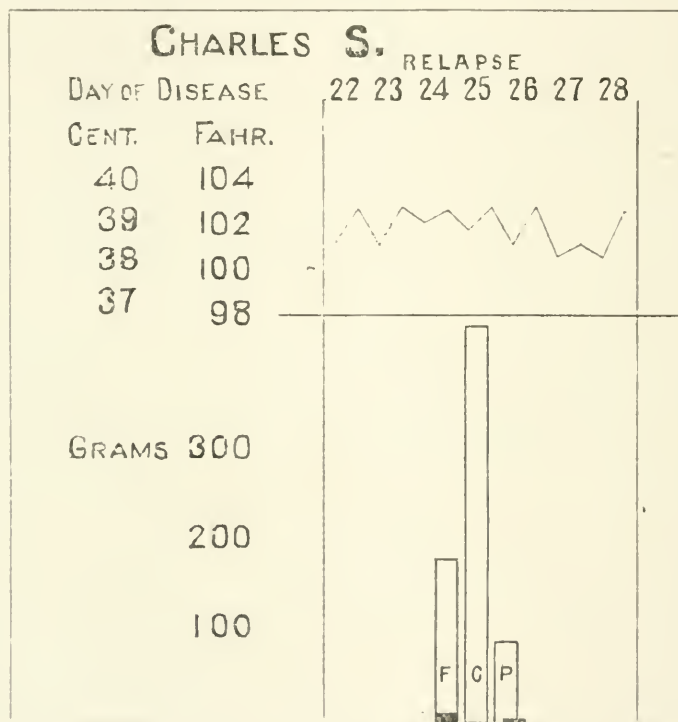


Chart 5.—Temperature curves, etc., in Case 5, Charles S.

that patients able to take the high calory diet seldom have diarrhea. Many patients who enter the hospital with marked diarrhea begin to have normal stools after they have been for a couple of days on the diet. During the total of seventy-two days studied, there were only six stools in addition to the results of the daily enemas and none of these was diarrheal. The charcoal and carmin powder used to mark off the periods appeared in the feces twenty-four hours after being swallowed with such regularity that it was deemed safe in two cases to omit the line of demarkation between some of the periods. The daily enemas contained semi-formed, yellow feces of practically normal appearance and odor. In

no case was there any blood in the stools. As routine the patients were given no medicine and no tubs, but were sponged for high temperatures.

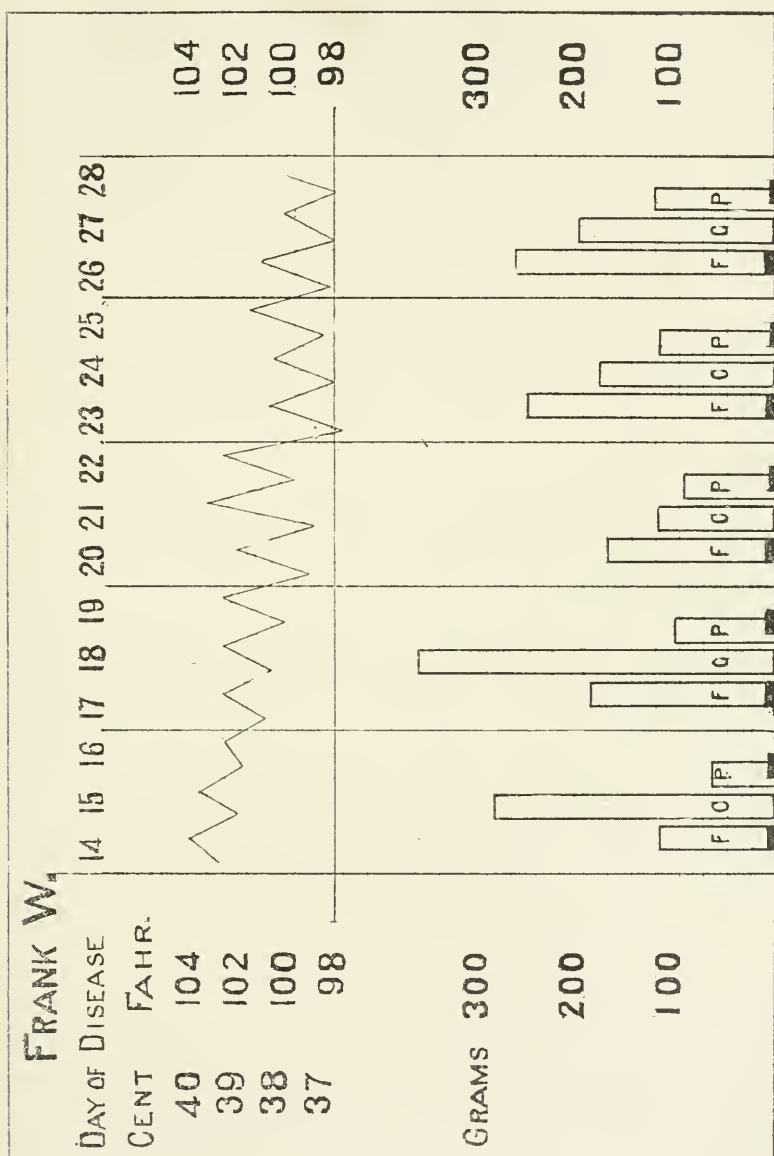


Chart 6.—Temperature curves, etc., in Case 6, Frank W.

Of the cases studied, three, Charles N., Michael K. and Frank W., were of rather mild type; three, Philip R., John N. and Charles S., were severe. It will be noted that a positive nitrogen balance was obtained in

every case during periods when the temperature was still high. One has difficulty in stating when convalescence begins in such cases. As soon as the temperature starts to show sharp morning remissions the patients look bright and seem comfortable. They read the newspapers, chat with their neighbors, eat their food with relish and rapidly gain weight and nitrogen-containing substances. Relapses are not more frequent on the high diet than on low diets, and it is only chance that four of these six patients had relapses. The cases were as follows:

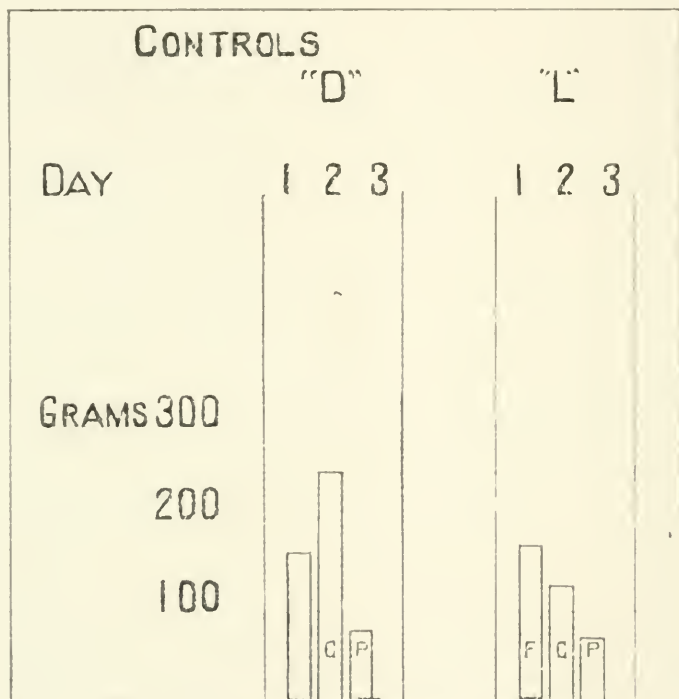


Chart 7.—Chart of control Cases "D" and "L."

CASE REPORTS

CASE 1.—Charles N., 60 years old, admitted Sept. 23, 1910, on the ninth day of the disease.

History.—The patient has been nursing three typhoid patients in his family. During the last four weeks he has been apathetic and at times dizzy. Date of onset of fever uncertain, probably nine days ago.

Physical Examination.—Well nourished elderly man. Right eye blind as a result of an old injury. Spleen palpable, several rose spots. Ninth to nineteenth day of disease. Temp. 101-103 F.; appetite good; takes 3,000 to 4,000 calories a day; no tympanites; mind clear; Widal test, negative. Nineteenth to twenty-first days, Period I. Twenty-second to twenty-sixth days feces discarded because they were overheated when drying. Twenty-seventh to thirty-fourth days, patient improving steadily; thirty-fifth day patient has severe pain in the head. Three days later the pain localized in the right eye which became much swollen. Diag-

nosis panophthalmitis. On the forty-first day the eyeball ruptured, discharging pus from which the typhoid bacillus was obtained in pure culture. By the forty-fifth day the eye was much improved and two days later the temperature reached normal. The patient made an uninterrupted convalescence.

CASE 2.—Michael K., 23 years old, admitted Oct. 13, 1910, on eighth day of disease.

History.—One week before admission the patient began to feel feverish and chilly and suffer from anorexia.

Physical Examination.—Fairly well nourished young man; apathetic; marked tympanites; rose spots present. Eighth to thirteenth days, temperature 101-104 F. Blood-culture shows typhoid bacilli. Appetite fair, takes 2,000 to 3,000 calories a day. No distention. Thirteenth day, feces collection started. Thirtieth day, temperature normal, convalescence rapid.

TABLE 2.—METABOLISM STUDY IN CHARLES N., CASE 1

Day of Disease	Calories			Food, Grams			Urine N + Feces N	Balance	Urine		Body Weight, Kilos
	Total	Per Kg.	Carboly- drates (per kg.)	Carboly- drates	Fat	Nitrogen			Vol., c.c.	Nitrogen	
19 (?) ..	4600	80	27	383	280	17.0				
20	3200	55	15	209	214	13.5	13.1	+ 0.4	1130	12.0
27	3910	68	16	226	268	19.2	760
28	4030	70	17	245	272	19.3	13.2	+ 6.1	1260	11.8
29	4090	71	14	195	302	19.0	11.5	+ 7.5	890	10.1
30	3720	64	16	222	253	17.6	11.3	+ 6.3	1060	9.9
31	4040	70	20	279	261	18.9	15.0	+ 3.9	1520	13.6	57.7
32	4040	70	16	226	261	18.7	1030
33	4670	81	22	314	311	19.2	12.3	+ 6.9	1290	11.1
34	3570	62	14	190	251	18.5	12.8	+ 5.7	1520	11.6	57.7
35	4410	76	19	261	305	19.5	14.6	+ 4.9	985	13.4
36	4300	75	16	223	312	19.8	11.8	+ 8.0	820	10.8
37	4520	78	19	266	312	20.8	13.3	+ 7.5	1415	12.3
38	4480	78	17	233	327	18.7	15.3	+ 3.4	1860	14.3
39	4060	71	16	227	284	19.2	15.2	+ 4.0	1500	13.4	57.5
40	4730	82	24	334	304	20.8	14.6	+ 6.2	1485	12.8
41	4420	77	18	247	311	20.1	12.0	+ 8.1	1200	10.2
42	4470	78	18	250	315	20.0	11.9	+ 8.1	1240	10.5
43	4170	72	18	253	274	22.7	750
44	4490	78	17	245	314	21.9	10.4	+11.5	1100	9.0	57.5

CASE 3.—Philip R., aged 23, admitted Oct. 19, 1910, on the seventh day of disease.

History.—For about three weeks the patient has felt chilly and feverish; headache severe; four to five watery stools daily; took to bed six days ago.

Physical Examination.—Fairly well nourished, pale, torpid, looks toxic; pulse small and weak; many rose spots; temperature 102-105 F.

Eighth to fifteenth days, experimental period: Twelfth day, pulse stronger, a few râles at bases of lungs; abdomen not distended. Thirteenth day, pulse weaker, patient given strychnin; slight distention. Seventeenth to twenty-second days, temperature dropping to normal; patient feels better. Twenty-third to twenty-seventh days, temperature rising in steps to 105 F.; pulse weaker. Twenty-seventh to thirtieth days, temperature 102-105 F. Thirty-first to thirty-fifth days, experiment resumed. Thirty-seventh day, temperature normal. Convalescence slow.

TABLE 3.—METABOLISM STUDY IN MICHAEL K., CASE 2

Day of Disease	Calories			Food Grams			Urine N + Feces N	Balance	Urine		Body-Weight, Kilos.
	Total	Per Kg.	Carbo- hydrates (per kg.)	Carbo- hydrates	Fat	Nitrogen			Vol., c.c.	Nitrogen	
8	1970	35	8	115	134	9.6
9	1970	35	8	115	134	9.6
0	2540	45	10	133	176	12.2	13.1	— 0.9	1155	12.2
1	2540	45	10	133	176	12.2	19.1	— 6.9	845	17.9
2	2370	42	11	151	154	11.3	Lost
3	2670	48	13	177	176	12.2	19.8	— 7.6	1940	18.6
4	3340	60	17	230	215	15.2	Lost
5	4410	79	27	374	257	19.2	13.4	+ 5.8	1710	11.6	55.9
6	3960	71	25	323	242	14.4	18.2	— 3.8	1820	16.4
7	4790	86	31	427	257	20.2	17.6	+ 2.6	1200	16.0

TABLE 4.—METABOLISM STUDY IN PHILIP R., CASE 3

Day of Disease	Calories			Food Grams			Urine N + Feces N	Balance	Urine		Body-Weight, Kilos.
	Total	Per Kg.	Carbo- hydrates (per kg.)	Carbo- hydrates	Fat	Nitrogen			Vol., c.c.	Nitrogen	
8	2400	44	9	123	166	13.9
9	2580	48	11	148	179	11.8
10	2470	45	11	143	175	12.1	16.8	— 4.7	1500	16.1	54.3
11	2830	52	14	186	179	15.8	17.2	— 1.4	1170	16.4
12	3100	57	13	178	215	15.3	19.7	— 4.4	1200	18.9
13	2890	53	14	180	191	14.5	20.8	— 6.3	1210	20.0
14	3460	63	17	230	225	17.2	14.9	+ 2.3	860	14.1
15	3810	70	16	214	268	17.9	14.9	+ 3.0	1340	14.1	54.7
31	2520	49	14	172	157	15.1	9.7	+ 5.4	900	8.8	51.8
32	2560	50	17	216	144	14.2	13.1	+ 1.1	1300	12.2
33	2900	56	19	242	160	17.6	13.9	+ 3.7	*	13.1
34	2880	56	26	310	135	14.4	9.5	+ 4.9	*	8.7
35	2920	59	20	245	159	18.2	14.0	+ 4.2	*	13.2	49.1

*Urine volumes made up to 2000 c.c.

CASE 4.—John N., aged 28, admitted Oct. 25, 1910, seventh day of disease. Died December 1.

History.—Onset six days ago with headache. Since then the patient has had anorexia and diarrhea.

Physical Examination.—Large frame, fairly well nourished, face flushed, abdomen flat, slight tenderness in left hypochondrium. A few rose spots were found.

Eighth day, blood culture shows typhoid bacilli. Tenth to eleventh days: slight soreness in abdomen and slight distention. Eighth to thirteenth days: temperature 101-104 F. Calories of food 2,500 to 3,500. Fourteenth to twenty-first days, temperature 100-103.6 F. Calories 3,600. Twenty-second to twenty-fifth days, temperature 102-105 F. Twenty-sixth to thirtieth days, period of investiga-

tion. Thirty-first to thirty-fourth days, temperature falling, patient more comfortable. Thirty-fifth day temperature shot up to 105 F. and a cough developed; during the next few days the left leg developed a boggy edema, the temperature remained high, signs of consolidation appeared in the left upper lobe. The patient became very toxic and died on the forty-fourth day of his illness.

CASE 5.—Charles S. (service of Dr. C. L. Dana), aged 21, admitted Aug. 5, 1911, fourth day of disease.

History.—Onset three days ago with chilly sensations and headache. Since then the patient has felt weak and feverish.

TABLE 5.—METABOLISM STUDY IN JOHN N., CASE 4

Disease Day of	Calories			Food Grams			Urine N + Feces N	Balance	Urine		Body Weight, Kilos
	Total	Per Kg.	Carbo- hydrates (per kg.)	Carbo- hydrates	Fat	Nitrogen			Vol., c.c.	Nitrogen	
26	3540	55	16	256	227	17.0	11.0	+ 6.0	750	10.0
27	4030	62	19	301	246	17.4	15.7	+ 1.7	800	14.7
28	3870	58	18	280	245	18.2	18.0	+ 0.2	1109	17.1
29	3880	59	22	349	221	16.9	16.4	+ 0.5	850	15.5
30	3870	58	16	247	246	19.6	18.3	+ 1.3	1009	17.4	64.8

TABLE 6.—METABOLISM STUDY IN CHARLES S., CASE 5

Day of Disease	Calories			Food Grams			Urine N + Feces N	Balance	Urine		Body Weight, Kilos
	Total	Per Kg.	Carbohy- drates (per kg.)	Carbohy- drates	Fat	Nitrogen			Vol., c.c.	Nitrogen	
22	2970	51	25	356.6	131.6	11.1	11.4	— 0.3	1255	10.2
23	4540	78	38	541.8	186.6	16.3	17.5	— 1.2	2350	16.3	58.2
24	5330	92	43	608.1	215.0	19.7	15.7	+ 4.0	1800	14.5
25	4240	73	33	463.5	205.9	16.8	12.5	+ 4.3	1650	11.3
26	2820	48	17	243.9	147.2	11.0	23.3	—12.3	2155	22.1
27	4450	77	33	465.5	195.0	15.4	14.5	+ 0.9	1110	13.3
28	4650	80	31	446.2	222.2	16.3	20.1	— 3.8	1220	18.9	58.2

Physical Examination.—Well nourished, abdomen flat, spleen palpable, a few rose spots.

Fourth to twelfth days, temperature 101-103 F.; appetite good; not very sick. Seventeenth to nineteenth days, temperature normal. Twentieth to twenty-third days, temperature rising again in steps. Twenty-fourth to thirty-eighth days severe relapse with temperature 102-104 F. On the twenty-fifth day a profuse nose bleed occurred, followed by several other severe attacks during the next two weeks. The patient became very anemic. The temperature fell slowly reaching normal on the sixtieth day. Convalescence was slow.

The respiratory quotients of this patient and of the following case, Frank W., were investigated by Dr. Coleman and myself. The results will appear shortly.

CASE 6.—Frank W., aged 27, admitted Nov. 23, 1911, on the tenth day of the disease.

History.—Nine days previously the patient began to have fever, headache and pains all over the body.

Physical Examination.—Small frame, 5 feet 4 inches tall, well nourished, prostrated, apathetic, spleen palpable, a few rose spots found.

Tenth to eleventh days: temperature 103-105 F.; appetite poor, diarrhea marked. Eleventh to thirteenth days, temperature 102 to 105 F.; diarrhea has ceased, appetite is improving. Fourteenth to twenty-eighth days, period of investigation. Appetite steadily improving; glucose was found in the urine in amounts which increased steadily until he passed 79 gm. on the nineteenth day. The carbohydrates of the food were then cut down until the sugar disappeared from the urine. The temperature fell steadily, reaching normal on the thirty-third day. The patient felt strong and was up in a chair when on the forty-seventh day from the onset the temperature began to rise and he went through a moderately severe relapse lasting fifteen days. On the seventh day of the relapse bilateral subconjunctival hemorrhages appeared but cleared up in a couple of weeks. Repeated urine tests during his rapid convalescence showed no sugar, although he was taking large amounts of carbohydrate.

Controls.—D and L. These were two healthy young men between the ages of 25 and 30. They were given the typhoid diet but could not take as large amounts of food as the patients.

TABLE 7.—METABOLISM STUDY IN FRANK W., CASE 6

Day of Disease	Calories			Food Grams			Urine N + Feces	Balance	Urine				Body Weight, Kilos
	Total	Per Kg.	carbohy- drates (per kg.)	Carbohy- drates	Fat	Nitrogen			Vol., c.c.	Nitrogen	Glucose	Creatinin	
...	1910	35	21	276.0	67.2	5.9	19.9	-14.0	1222	18.5	Tr.	1.67
...	3380	62	25	333.7	169.2	16.9	16.6	+ 0.3	1210	15.2	7.72	1.28	54.5
...	2510	46	20	267.2	125.1	9.7	15.7	- 6.0	1052	14.3	8.03	1.27
...	3700	68	26	342.7	198.7	17.4	20.3	- 2.9	1455	18.9	15.48	1.35
...	3860	71	30	397.3	192.0	17.2	21.3	- 4.1	1675	19.9	31.6	1.59
...	3690	69	28	373.0	190.3	15.4	19.3	- 3.9	1800	17.9	79.6	1.29	53.6
...	3025	57	13	173.1	202.1	17.0	14.8	+ 2.2	1765	13.8	11.0	.99
...	2670	50	10	127.7	183.0	17.1	20.9	- 3.8	2050	19.9	8.5	1.17
...	1860	35	5	65.4	139.3	11.1	13.9	- 2.5	780	12.9	0.0	1.05
...	2860	54	10	131.4	200.3	17.9	19.7	- 1.8	1545	18.8	0.0	1.11	52.7
...	3980	76	16	201.5	282.4	20.5	17.4	+ 3.1	1575	16.5	0.0
...	4100	78	17	218.0	288.3	20.6	15.2	+ 5.4	1475	14.3	1.6	1.12	52.5
...	3750	71	15	195.3	264.7	19.0	12.7	+ 6.3	1300	11.9	1.64
...	3740	71	16	203.4	257.3	20.1	13.1	+ 7.0	1540	12.3	1.8	1.06
...	4100	76	16	215.0	287.6	21.1	18.2	+ 2.9	1790	17.4	1.6	1.29	53.9

METHODS

The patients were under the direct care of the head nurse, Miss Mary E. Sheehan, who has helped in metabolism experiments on typhoid cases for the last three years. All food given was measured and recorded. Samples of the milk and cream were analyzed from time to time and the other foods were prepared according to known recipes and their food values calculated from the tables of Atwater and Bryant. (Bull. 28, U. S. Department of Agriculture.)

Every morning the nurse gave an enema of about 250 c.c. of warm water containing 0.75 gm. soap, which amount was, of course, subtracted from the fatty bodies found by analysis in the resulting stool. The results from these enemas were very uniform except in the case of Charles S., in whom an attempt was made to use salt solution instead of the usual soap enema. There was so much retention of feces in the lower bowel for the first three days that soap enemas were again resorted to and the period lengthened to seven days in order to get accurate results.

The periods were marked off at first by a teaspoonful of charcoal, which was somewhat difficult to recognize in the enemas. Later carmin powder in doses of 0.3 gm. was used and a most satisfactory line of demarkation obtained. In two of the earlier cases in which the food and stools were very uniform, the demarkation was omitted as the patients objected to the charcoal.

As soon as the initial dose of charcoal or carmin was given, all urine was saved and all the feces as soon as the line of demarkation appeared. The enemas and feces were dried at a temperature below 100 C. with the addition of alcohol. The several stools of each period were then united, powdered, passed through a fine sieve and analyzed.

It was feared that the process of drying, which required one or two days, might cause a loss of some of the constituents. To determine this a normal man was put on the high calory typhoid diet and some of the formed stools thoroughly mixed and samples analyzed fresh and after drying in the above manner. The results show that the changes are negligible.

TABLE 8.—ANALYSES BEFORE AND AFTER DRYING, EXPRESSED IN PER CENT. OF MOIST STOOL IN CONTROL CASE

	Fresh Feces	Dried Feces	Error Caused By Drying
Fat.....	4.20	4.38
	4.34	4.43
Average.....	4.27	4.405	+3.2
Carbohydrate.....	.97	.92
	.97	.94
Average.....	.97	.93	—4.0
Nitrogen.....	.829	.822
	.874	.827
	.860	.828
Average.....	.8543	.8257	—3.3

All analyses were made in duplicate and if the results did not agree, were repeated until satisfactory. The nitrogen was determined by the Kjeldahl method, the fats by the complicated but exact method of Kumagawa and Suto,¹⁰ which determines the fats, fatty acids and soaps

10. Kumagawa and Suto: Ein neues Verfahren zur quantitative Bestimmung des Fettes und der unverseifbaren Substanzen in tierischem Material nebst der Kritik einiger gebräuchlichen Methoden. *Biochem. Ztschr.*, 1908, viii, 212; Inaba, R.: Ueber die Fettbestimmungen des Faeces und einiger Nahrungsmittel nach der neuen Methode von Kumagawa-Suto. *Biochem. Ztschr.*, 1908, viii, 348.

together. Results obtained by this method are usually higher than by the older methods of ether extraction which have been shown to be very faulty.

The carbohydrate determinations gave a great deal of trouble. It is impossible to make an accurate sugar test without decolorizing the feces, and many of the methods of decolorization remove sugar as well as color. The dried feces contained from 2 to 4 per cent. carbohydrates and after the processes hydrolizing and decolorizing, the remaining solution for analysis contained about .05 per cent. dextrose. Accurate sugar determinations with such dilute solutions are difficult.

Various methods of decolorization were tested, using the Allihn method, and the Pavy method as modified by Kumagawa and Suto:¹¹ 0.25 gm. dextrose (Kahlbaum) was added to 4-gm. samples of a specimen of dried feces which gave no reduction after boiling with water, although it did reduce after hydrolizing with 2 per cent. HCl. The sample of feces with the added dextrose was boiled five minutes with 80 c.c. distilled water, cooled, 10 c.c. 20 per cent. HCl solution added and made up to 100 c.c. Two samples were filtered with difficulty, and Allihn determinations made with the highly colored filtrate. The others were decolorized by the mercuric nitrite method of Patein and Dufau¹² by basic lead acetate, mercuric bichlorid¹³ and by acid charcoal.

TABLE 9.—DECOLORIZATION TESTS OF FECES IN CONTROL CASES

Decolorized by	Sugar Method	Per Cent. Error in Tests,
Mercuric bichlorid	Allihn	-11., +.09
Mercuric bichlorid	Pavy	+9.5, +2.6, -0.2
Mercuric nitrate	Allihn	+3.6, +5.4
Mercuric nitrate	Pavy	-10.5, -5.9
Basic lead acetate	Allihn	-7.2, -5.8
Basic lead acetate	Pavy	-7.9, -15.6
Acid charcoal	Allihn	-10.8, -5.8, +.08, +5.2, +2.8, Av. -1.7.
Acid charcoal	Pavy	-11.0, -10.9, -5.1
Filtering; no decolorization	Allihn	-11, +0.9

It was clear that no method gave absolutely satisfactory results, but that the error of any method was not great enough to make a significant difference in the findings. When one considers that many carbohydrate determinations in feces are made by the grossly inaccurate method of subtracting the total weight of fat, protein and ash from the weight of

11. Kumagawa and Suto: Ein Beitrag zur Zuckertitrierung mit ammoniakalischer Kupferlösung nach Pavy. Beitr. z. wissenschaft. Med. u. Chem. (Salkowski's Festschrift), Berlin, 1904, 211.

12. Patein and Dufau. Method described in Abderhalden, Handb. d. Biochem. Arbeitsmethoden, ii, 183.

13. Ibid., p. 184.

the dried stool, one becomes reconciled to a smaller acknowledged error. The method finally chosen for analysis was the acid charcoal method which seemed more accurate and simpler than any of the others. A specimen of 3 to 4 gm. of powdered feces was boiled one and one-half hours in 100 c.c. 2 per cent HCl, in order to hydrolyze the starches into sugars. After cooling, the solution was made up to volume, about 4 gm. of the best quality animal charcoal added, filtered, 2 gm. more charcoal added, filtered, an aliquot portion rendered slightly alkaline with NaOH to precipitate the phosphates, made up to volume and filtered. With 50 c.c. of the clear filtrate, Allihn tests were made. In a few cases, the modified Pavy method was used.

Soluble carbohydrates were tested for by boiling a similar sample of feces with water and acidifying after the solution had cooled. Charcoal was then used for decolorization and an Allihn test made. In no case was there more than a very slight reduction. It is an interesting fact that the feces of Michael K., who for his first two periods was given no carbohydrate except lactose, gave 0.4 and 1.2 gm. "carbohydrate" after hydrolyzing, but none after plain boiling. Some reducing body or bodies other than carbohydrates must give this misleading result. Possibly mucin caused the reduction.

The indican was tested for in a roughly quantitative manner by Folin's method.¹⁴ One one-hundredth part of the total urine was treated with an equal volume of Obermeyer's reagent and the indigo blue extracted with 5 c.c. of chloroform and compared with Fehling's solution, which was given arbitrarily the value of 100. The color comparisons were made with Fehling's solution diluted to different percentages and were not made in a colorimeter. This method seems greatly preferable to the old method of recording the result in plus marks. Folin's normal individuals were on a diet very similar to the high calory diet and the indican excretion measured in this method ran between 12 and 140, the average of all six cases being 77.

Glucose in the urine was determined by Benedict's method,¹⁵ which gave most satisfactory results.

SUMMARY

Carbohydrates when given in amounts under 300 gm. a day were present in the stools only in traces, if, indeed, they were present at all. When amounts larger than 300 gm. were given, the stools sometimes contained 2 or 3 gm. of reducing bodies.

14. Folin: Analyses of Thirty "Normal" Urines. *Am. Jour. Physiol.*, 1905, xiii, 53.

15. Benedict, S. R.: The Detection and Estimation of Glucose in Urine. *Jour. Am. Med. Assn.*, 1911, lvii, 1193.

TABLE 10.—COMPARISON OF RESULTS.
CONTROLS

	Fat			Carbohydrate			Nitrogen			Indican in Urine
	Grams in Food	Grams in Feces	Per cent. Loss	Grams in Food	Grams in Feces	Per cent. Loss	Grams in Food	Grams in Feces	Per cent. Loss	
.....	172	6.4	3.8	127	.65	0.5	11.6	0.57	5.0	...
.....	164	3.1	2.0	249	.25	0.1	12.7	1.00	7.8	...
.....	CHARLES N.									
.....	247	24.3	9.8	296	1.2	0.4	15.2	1.06	7.0	100
.....	281	19.4	6.8	222	1.0	0.4	19.2	1.44	7.5	90
.....	258	25.1	9.7	242	1.0	0.4	18.4	1.44	7.8	20
.....	289	14.9	5.2	255	0.8	0.3	18.8	1.22	6.5	20
.....	317	19.6	6.1	241	1.1	0.4	19.5	1.00	5.1	20
.....	300	16.9	5.6	269	1.2	0.4	20.0	1.78	8.9	20
.....	301	14.8	4.9	249	1.1	0.4	21.5	1.37	6.4	30
.....	PHILIP R.									
.....	173	14.5	8.4	138	0.4	0.28	12.6	0.68	5.4	100
.....	215	11.7	5.5	198	0.4	0.20	16.1	0.78	4.8	120
.....	150	6.5	4.3	194	0.4	0.23	14.6	0.86	5.9	80
.....	151	6.3	4.2	266	0.6	0.23	16.7	0.92	5.5	90
.....	MICHAEL K.									
.....	148	16.6	11.2	121	0.4	0.3	10.5	0.92	8.8	50
.....	169	16.2	9.5	154	1.2	0.8	11.9	1.20	10.0	110
.....	238	11.7	4.9	309	2.4	0.6	16.3	1.79	11.0	70
.....	257	11.4	4.4	427	2.8	0.6	20.2	1.61	8.0	30
.....	JOHN N.									
.....	236	9.8	4.2	278	0.75	0.3	17.2	0.91	5.3	105
.....	237	8.4	3.5	292	0.78	0.3	18.2	1.03	5.7	90
.....	CHARLES S.									
.....	186.1	15.8	8.5	446.5	1.21	0.27	15.2	1.16	7.6	50
.....	FRANK W.									
.....	120.7	7.9	6.5	292.3	0.93	0.32	10.8	1.40	13.0	15
.....	193.7	10.8	5.6	371.0	0.58	0.15	16.7	1.42	8.5	60
.....	174.8	10.2	5.8	122.1	0.51	0.12	15.2	1.01	6.6	25
.....	257.0	9.0	3.5	183.8	0.53	0.29	19.0	0.88	4.6	25
.....	269.9	10.0	3.7	204.6	0.74	0.36	20.1	0.84	4.3	25

The nitrogen of the feces averaged 1.12 gm. a day, and never exceeded 1.8 gm., amounts which are within normal limits. The percentage loss was 7.1 per cent., which is a figure lower than that of previous observers. This, perhaps, may be due to the fact that the diet was less irritating to the intestinal tract.

With the fats there seems to be a diminution of both the percentage loss and the actual weight of fat in the feces as the disease progresses. It is hard to give averages which are fair, but it can be said that during the first three weeks of the attack and during the height of a relapse, the patients lose on an average 7.2 per cent. of the ingested fat. Later in the disease, with a falling temperature and decreasing toxemia, they lose about 4.5 per cent. The average loss for all cases examined was 6.02 per cent., which, though higher than the normal figure of 3 per cent. for a similar diet, is not enough higher to be of any clinical significance. The dried feces contained from 30 to 50 per cent. fat. It must be remembered that very large amounts of fat were given.

The stools of typhoid fever patients on the high calory diet resemble normal stools very closely. The indican of the urine, which is rather high during the early part of the disease, decreases steadily as the patient's condition improves. The indican excretion compares favorably with that of Folin's normal individuals.¹⁴

The work of Shaffer and Coleman in establishing nitrogen equilibrium in typhoid fever has been confirmed.

CONCLUSIONS

Typhoid patients throughout the disease can absorb carbohydrates and protein as well as normal individuals. They can absorb very large amounts of fat, but the percentage of absorption is somewhat lower than the normal, especially in the earlier part of the disease.

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THE EFFECT OF A SKIN IRRITANT ON THE LOCAL BLOOD-FLOW IN THE HAND*

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It is common knowledge that skin irritants produce reddening of the skin, which may under certain circumstances be followed by the appearance of vesicles, pustules, or a diffuse dermatitis. The effect on the general and the local circulation has been particularly studied in the case of carbon dioxid baths, which differ from most other baths in that they produce a local reddening of the skin. According to O. Miller and his collaborators¹ the reddening of the skin which occurs in these baths is a cutaneous phenomenon and it is not associated with a relaxation of the deeper arteries. Strasburger,² who sought to avoid the technical difficulties of working with carbon dioxid baths, added spirits of mustard (*Senfspiritus*) to the water which surrounded the arm in a plethysmograph and he found that when the arm assumed a red color comparable to that seen in the carbon dioxid bath, the arm had increased 4 to 12 c.c. in volume. Yet we doubt if binding conclusions concerning the local blood-flow can be drawn either from changes in arm volume or from variations in the form or size of the pulse; for these do not necessarily indicate the degree of constriction of the finer arterioles, a condition which seems to exercise a predominating influence on the local rate of flow.

It seemed advisable, therefore, to study the effect of skin irritants, using the methods recently described by G. N. Stewart³ and by Hewlett and Van Zwaluwenburg⁴ for determining the rate of blood-flow in the hand and in the arm. Unfortunately neither method is well adapted for studying the local effects of carbon dioxid baths. The evolution of gas excludes the plethysmograph method of Hewlett and Van Zwaluwenburg, and the chemical reaction in the artificial bath would probably interfere with Stewart's calorimetric method. Our experiments have therefore been limited mainly to the effect of baths containing irritating

*From the Department of Internal Medicine, University of Michigan.

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1. Müller, O., and Veiel, E.: Beiträge zur Kreislaufphysiologie des Menschen, besonders zur Lehre von der Blutverteilung. Samml. klin. Vortr., 1911, In. Med. 194, 195, 196, 199, 200, 201. (Literature.)

2. Strasburger, J.: Einführung in die Hydrotherapie und Thermotherapie, 1909, Jena, 243.

3. Stewart, G. N.: Studies on the Circulation in Man. Heart, 1911, iii, 33.

4. Hewlett, A. W., and Van Zwaluwenburg, J. G.: The Rate of Blood Flow in the Arm. Heart, 1909, i, 87.

quantities of mustard, though a few experiments with salt mixtures such as are used in certain Neuheim baths were also performed. In order to ascertain the effect of the irritants, determinations were made simultaneously on the two hands while one was exposed to water containing the irritant and the other to ordinary tap water. In this manner it was possible to eliminate the variations in flow which occur in a single individual at different times. Scrupulous care was taken to maintain the two water baths at the same temperature in order to exclude the effect of local variations in temperature.⁵ The results of our experiments are shown in the accompanying tables.

TABLE 1.—EFFECT OF MUSTARD BATH ON LOCAL BLOOD-FLOW IN THE ARM
(Plethysmographic Method)

Subject	Room Temp.	Water Temp.	Average Rate of Flow		Remarks
			Mustard	Control	
....	C.	C.		
Weis ...	24	34	9.2*	6.2	Arm exposed to mustard felt very warm.
Weis ...	23	33	6.7	2.2	Arm exposed to mustard felt very warm and later smarted considerably. It became swollen the following night and subsequently the skin desquamated.
Wood ...	22	32.5	3.0	4.2	Arm exposed to mustard felt warm.
Wood ...	18	33	2.9	3.5	Arm exposed to mustard felt warm with slight smarting.

*These figures represent averages of five or more determinations.

TABLE 2.—EFFECT OF MUSTARD BATH ON LOCAL BLOOD FLOW IN THE HAND
(Calorimetric Method)

Subject	Room Temp.	Water Temp.	Average Rate of Flow		Remarks
			Mustard	Control	
....	C.	C.		
Wood ...	17.5	31	8.3	8.4
Wood ...	20.5	30	6.0	5.3
Weis ...	18.5	31	4.8	6.8
Weis ...	20	30	3.3	4.5
Weis ...	20.5	30	3.2	5.9
Weis ...	21.5	30.5	8.5	7.6
Weis ...	25.5	31.5	9.7	10.6	Hand exposed to mustard smarted but was not reddened.
Weis ...	27	30.5	4.5	7.0	Hand exposed to mustard was reddened and smarted.
Weis ...	28	31.8	14.0	13.0	Hand reddened and burned and showed slight dermatitis six hours later.
Weis ...	28.4	30.5	8.5	11.9	Hand is mustard reddened and smarted.
Weis ...	30.2	31.4	18	17.4	Hand slightly reddened and smarted.
Weis ...	30.5	32	14.4	16.9	Hand smarted and was considerably reddened.
Kinde ...	13.0	29.5	3.1	3.4
Kinde ...	14.5	30.5	13.1	11.9	Hand smarted and reddened.
Kinde ...	15	29.3	8.2	9.0
Kinde ...	15.5	30.0	5.0	4.2
Kinde ...	18	29	5.5	6.7
Kinde ...	19	30.5	6.3	7.4	Hand reddened.
Kinde ...	19.5	29.5	8.8	7.7
Kinde ...	20.5	29.5	6.2	6.3
Kinde ...	21	29.8	6.1	5.3	Hand reddened.
Kinde ...	23	30.0	17.0	10.5

5. Hewlett, A. W., Van Zwaluwenburg, J. G., and Marshall, M.: The Effect of Some Hydrotherapeutic Procedures on the Blood-Flow in the Arm. *THE ARCHIVES INT. MED.*, 1911, viii, 591.

A typical protocol of this group of experiments follows:

CALORIMETRIC DETERMINATION OF THE RATE OF BLOOD-FLOW IN THE HAND

(Weisman—subject; Wood—operator.) April 23, 1912.

Thermometer (L) in right calorimeter.

Thermometer (S) in left calorimeter.

Mustard water in right calorimeter.

Tap water in the left calorimeter.

The right hand was soaked in mustard water at 30 C. for seventeen minutes and the left hand in tap water at the same temperature for the same length of time, immediately preceding the experiment. The right hand smarted but was not reddened. Room temperature, 25.5 C.

PRELIMINARY READING IN CALORIMETERS TO DETERMINE RATE OF HEAT LOSS

Right Calorimeter		Left Calorimeter	
Time	Readings	Time	Readings
1.15	1.540	1.15	3.220
1.16	1.560	1.16	3.240
1.17	1.590	1.17	3.260
1.18	1.620	1.18	3.285
1.19	1.660	1.19	3.310
1.20	1.690	1.20	3.330

Temperature of water in each, 30 C.

READINGS AFTER INSERTION OF THE HANDS IN CALORIMETER

Right Calorimeter		Left Calorimeter	
Time	Readings	Time	Readings
1.24	1.360	1.24	2.970
1.25	1.270	1.25	2.860
1.26	1.118	1.26	2.740
1.27	1.100	1.27	2.630
1.28	1.030	1.28	2.530
1.29	0.950	1.29	2.430
1.30	0.890	1.30	2.360
1.31	0.810	1.31	2.260
1.32	0.740	1.32	2.160
1.33	0.650	1.33	2.070
1.34	0.590	1.34	2.015
1.35	0.535	1.35	1.950

Temp. 31.5 C.

Temp. 31.5 C.

HEAT LOSSES FROM CALORIMETERS AFTER THE HANDS HAD BEEN TAKEN OUT

Right Calorimeter		Left Calorimeter	
Time	Readings	Time	Readings
1.40	0.570	1.40	1.930
1.41	0.600	1.41	1.955
1.42	0.640	1.42	1.980
1.43	0.665	1.43	2.015
1.44	0.700	1.44	2.045
1.45	0.720	1.45	2.080

Weight of mustard solution 1615 gm.

Weight of water 1639 gm.

Weight of right calorimeter 470 gm.

Weight of left calorimeter 470 gm.

Volume of the hand substance 485 c.c. (right).

Volume of the hand substance 510 c.c. (left).

In the experiments with mustard, the specific heat of the mustard solution was regarded as equivalent to that of an equal weight of water.

In the experiments in which the salt solution was used, however, the specific heat was determined by multiplying the actual weight of the solution in grams by .93. Similarly in the following calculations, the actual weights of the calorimeter and of the hand substance were reduced to their water equivalents.

CALCULATION OF THE RATE OF BLOOD-FLOW IN THE RIGHT HAND

Calorimeter correction for heat loss in ten minutes.....	.30
With hands in calorimeter for ten minutes the temperature rose to.....	.735

Total rise 1.035

Water equivalent of the mustard solution 1615

Water equivalent of hand substance..... 388

Water equivalent of calorimeter 52

Total water equivalent 2055

Total calories given off from hand in ten minutes= $2055 \times 1.035 = 2126.9$.

Total calories given off from hand in one minute= 212.69 . $Q = \frac{H}{T - T^1} \times \frac{1}{S}$

Where Q equals the quantity of blood in grams flowing through the hand in the time of the experiment, H=the heat given off by the hand, T=the temperature of the arterial blood, T¹=the temperature of the water, S=the specific heat of the blood.

$$Q = \frac{212.69}{36.5 - 31.5} \times \frac{1.0}{.9} = 47$$

Rate of blood-flow per minute per 485 c.c. hand substance=47.

Rate of blood-flow per minute per 100 c.c. hand substance=9.7.

CALCULATION OF THE RATE OF BLOOD-FLOW IN THE LEFT HAND

Calorimeter correction for heat loss in ten minutes.....	.26
With hands in calorimeter for ten minutes temperature rose.....	.909

Total rise 1.169

Water equivalent of water..... 1639

Water equivalent of hand substance..... 408

Water equivalent of calorimeter 52

2099

Total calories given off from hand in ten minutes= $2099 \times 1.169 = 2453.731$.

Total calories given off from hand in one minute=245.373.

$$Q = \frac{245.373}{36.5 - 31.5} \times \frac{1.0}{.9} = 54.5$$

Rate of blood-flow per minute per 510 c.c. hand substance 54.5

Rate of blood-flow per 100 c.c. hand substance (per minute)..... 10.6

Rate of blood-flow in mustard solution..... 9.7

Rate of blood-flow in water..... 10.6

Difference9

TABLE 3.—EFFECT OF SALT BATHS* ON THE LOCAL BLOOD-FLOW IN THE HAND

Subject	Room Temp.	Water Temp.	Average Rate Flow Salt	Control
.....	C.	C.
Kinde	20	28.5	6.4	7.0
Kinde	20.5	29.8	9.7	7.0
Kinde	21	30.5	9.3	9.7
Kinde	21	30.5	9.2	7.8

*The salt bath contains Na Cl (5 per cent), Ca Cl₂ (.5 per cent).

These experiments indicate the considerable variations in the blood-flow of the hand or arm which may occur in a single individual at different times. Such variations are due in part to the temperature of the room⁶ and in Table 2 in which the results for each individual are arranged according to room temperatures it will be seen that there is a very definite tendency for the rate to increase on days when the experiments were conducted in a warm room even though the hands were always exposed to water of about the same temperature. It is also evident, however, that other factors than room temperature must have been active to account for the variations from the rule that the rates increase with higher room temperatures. Exactly what these other factors are we have not determined.

So far as we have been able to determine, no definite effect on the local blood-flow results from irritation of the skin by mustard or the salt mixture used. Only in the second experiment of Table 1 was a very marked result obtained and this was associated with a rather severe burn from the mustard which left a dermatitis that did not heal for days. Some doubt is thrown on this experiment by the unusually slow rate in the control arm. Aside from this case the faster of the two hand rates seldom exceed the slower by more than 50 per cent, and the difference was about as often in one direction as in the other. It must be admitted that our results throughout are less concordant for the two hands than are those published by Stewart and it is possible that with better technic we should be able to demonstrate some constant difference between the hand exposed to the irritant and the one not so exposed. We feel safe in asserting, however, that the effect if present is but slightly relative to the very marked variations in the blood-flow produced by thermic and by other influence. Certainly it could not be objected that our failure to obtain more marked results was due to insufficient irritation of the skin. In the earlier experiments the hand was exposed to the mustard bath only during its stay of about fifteen minutes in the calorimeter, but in the latter experiments a preliminary soaking in a mustard bath for fifteen minutes or more usually produced redness and smarting before the determination itself was made and these were increased during the determination. We always attempted to stop short of producing a definite dermatitis, but in two experiments at least (No. 2 of Table 1, and No. 9 of Table 2) this occurred. The former has already been alluded to; the latter was not associated with a definitely increased blood-flow during the bath.

Two explanations might be offered for the fact that a local reddening of the skin is not associated with an increased rate of flow in the hand.

6. Hewlett, A. W.: The Effect of Room Temperatures Upon the Blood-Flow, Etc., *Heart*, iii, 1911, 230.

In the first place it is possible that although the flow through the skin is increased the flow in the deeper structures of the hand is proportionately diminished so that the resultant of the two is *nil* or nearly *nil*. In the second place the reddening may be due to a dilatation of the small cutaneous capillaries and veins, while the arterioles which are believed to exercise a predominating influence on the local flow are unaffected. We incline toward the latter explanation chiefly for the reason that when the flow in both hands was slow the hand exposed to mustard frequently showed a slightly cyanotic color, which would indicate that the cutaneous vessels were dilated, but that the flow through them was not sufficiently fast to bring much arterial blood to the surface.

CONCLUSIONS

1. Irritation of the skin by a mustard bath short of producing a definite dermatitis does not materially increase the rate of blood-flow through the hand relative to the hand whose skin is not so irritated.
2. The local redness is probably due to a dilatation of the cutaneous capillaries and venules without a corresponding dilatation of the underlying arterioles.

CONCERNING THE PRESENCE IN URINE OF CERTAIN PRESSOR BASES *

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Probably the first work on the presence of toxic alkaloid-like bases in putrid meat and urine, and their significance for purposes of diagnosis in disease, was done by Selmi in 1880. In 1884 Bouchard began his development of the idea of urinary toxicity as measured by biological experimentation, and its application to clinical problems. Bouchard's work, and that of other French writers, gave an impetus to the investigation of the chemical character of the toxic elements in urine; and in this connection, attention became directed particularly toward those of a basic alkaloid-like nature, and many such have been identified.¹

In 1906 Abelous² directed attention to a certain phase of this subject, by isolating from putrid meat a substance, basic in nature, which, when injected into animals, produced a pronounced rise in blood-pressure. He was unable to identify this base with any degree of accuracy, but assigned to it the provisional formula $C_6H_{11}NO_3$. Rosenheim,³ in 1909, found that from the products of the putrefaction of fresh human placentas he could isolate two pressor principles which were identical, both physiologically and in melting-point and crystallization, to two substances isolated about the same time by Barger and Walpole from putrid meat, by a somewhat different process than that used by Abelous. However, Barger and Walpole,⁴ by using large quantities of meat, were able to obtain these pressor bases in sufficient amount to identify them as isoamylamine and parahydroxyphenylethylamine, which made it probable that they were formed by bacterial decomposition from leucin and tyrosin, respectively, by the splitting off of CO_2 . In 1908 Abelous reported that he had isolated from normal urine a basic substance, soluble in ether, which physiologically was apparently identical with the base he obtained from putrid meat.⁵ In 1909 Bain⁶ reported having obtained from normal urine, two pressor

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1. For a critical review of the earlier literature on this subject, reference can be made to Kutscher's article in Abderhalden's *Handbuch der Biochemischen Arbeitsmethoden*, 1910, 111-2, 863; and to that of Ackermann 2, p. 1002.

2. Abelous: *Compt. rend. Soc. de biol.*, 1906, ix, 463; *ibid.*, 1906, ix, 531.

3. Rosenheim: *Jour. Physiol. (Eng.)* 1909, xxxviii, 337.

4. Barger and Walpole: *Jour. of Phys. (Eng.)* 1909, xxxviii, 343.

5. Abelous: *Compt. rend. Soc. de biol.*, 1909, lxy, 848; *ibid.*, 1909, lxy, 596.

6. Bain: *Lancet (London)*, 1909, ii, 365, *ibid.*, 1910, i, 1190; *ibid.*, 1911, i, 1409.

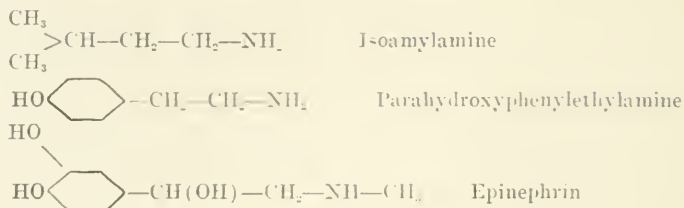
substances, one soluble in ether, presumably isoamylamine, the other soluble in amyl alcohol and supposedly parahydroxyphenylethylamine. He further found that in several cases of high blood-pressure, these pressor principles were either entirely absent from the urine or in greatly diminished amounts; that on a mixed diet they were in greatest quantity, and greatly lessened if the person whose urine was used was on a vegetable diet. Bain also noted that the bases were absent from children's urine up to the age of 12, and began to be excreted about the fourteenth year. Similar observations had previously been made by Abelous with his urinary extract, which he terms "Urohypertensine."⁵

Barger and Dale⁷ have shown that the watery extracts of ergot are very similar in melting-point and crystallization to parahydroxyphenylethylamine, and that their physiological action is practically identical. Such a preparation has been put on the market by Burroughs, Wellcome and Co., under the trade name "Tyramine," .005 gm. of which, when injected into animals, gives quite a pronounced rise in blood-pressure. Dale and Dixon⁸ worked on the physiological action of isoamylamine and parahydroxyphenylethylamine, obtaining, in brief, the following results: When injected into cats under ether anesthesia, they both cause a distinct rise in blood-pressure, but much less than epinephrin, the curve rising and terminating more slowly than the latter, with a longer latent period. Of the two, isoamylamine is the less powerful. Both cause an increase in the output of the heart by increasing the rate and amplitude of the beat. Isoamylamine produces a primary depression, parahydroxyphenylethylamine does not. When injected into the circulation, both cause a reflex inhibition through the vagi, with a marked diminution in the rate of outflow from the vessels of the periphery and intestine. Isoamylamine further causes a constriction of the vessels of the lungs, and a slight constriction of the bronchioles. Both cause a contraction of the pregnant uterus and inhibit activity of the non-pregnant organ, the same as epinephrin, although labor was not induced by administration made a week before term. Both substances cause a dilatation of the pupil, protrusion of the eye-ball and secretion of tears. They act when given either hypodermatically or by mouth, and they are absorbed more readily through the alimentary canal than is epinephrin. Their action is not strictly, but mostly, limited to the periphery and there confined to muscles and glands receiving a sympathetic supply. By a comparison of the structural

7. Barger and Dale: *Jour. Physiol. (Eng.)* 1909, xxxviii, 77.

8. Dale and Dixon: *Jour. Physiol. (Eng.)*, 1910, xxxix, 25.

formulæ of the bases with that of epinephrin, the similarity can further be noted :



Harvey⁹ recently reported some interesting effects of the prolonged ingestion of parahydroxyphenylethylamine by animals. He both fed and injected rabbits daily with a 2 per cent. solution of this substance over a period varying from eighty to 300 days, gradually increasing the amount. He then killed the animals and found that out of thirty-three, twenty had developed renal lesions, in twenty-five there were lesions in the mesial coats of the arteries, and in ten the heart was enlarged and fibrous. His work, however, is open to criticism, in that he fails to state the source of the "parahydroxyphenylethylamine" used in his experiments, the inference being that "Tyramine" was the substance employed. We do not know that chemically this is the same as the supposed parahydroxyphenylethylamine isolated from normal urine.

The significance of the work of Abelous, Bain, Harvey and others concerning these pressor bases, is apparent if corroborated. It strongly suggests the possibility that certain diseased conditions which manifest a tendency to high blood-pressure, notably arteriosclerosis and nephritis, may be caused by the formation and absorption of putrefactive pressor bases in the intestine. Furthermore, the work which has just been reviewed, would tend to indicate that even in health some formation of pressor bases occurs, and it would be plausible enough to assume that under certain conditions of diet or disease the amounts of these substances would be found greatly augmented; and again, that if some method were at hand for measuring them, the amount of putrefactive bases in the urine might be made a useful clinical index of the extent to which this variety of poisoning was going on. The possibility suggests itself also, that an increase in the amount of putrefactive bases absorbed by the body, might be responsible not only for the chronic diseases with high blood-pressure and organic changes in the kidneys and cardiovascular apparatus, but for certain other symptoms as well, the causes of which are at present little understood, among which may be mentioned the so-called constipation headaches, asthma and perhaps certain cutaneous disturbances. Much of value in diagnosis, prophylaxis and clinical knowledge would seem to be involved in a study of this problem.

Working toward a solution of these things we should have to go to the beginning and ask, Are these bases, isoamylamine and parahydroxy-

9. Harvey: Path. and Bact. (Eng.), 1911, xliii, 95.

phenylethylamine, formed in the intestine? Thus far this question cannot be answered positively, for they never have been isolated from the feces and analyzed as such, although Abelous in attempting to find where his "Urohypertensine" was formed, took 450 gm. of intestinal contents and treated it with three times its volume of alcohol. By extracting in the same way as with his method of urine extraction, he was able to obtain a pressor substance, so he assumes that it is formed in the intestinal canal.¹⁰ We must remember, however, that Abelous' "Urohypertensine" has never been identified chemically. Color is given the idea by an experiment performed by Barger and Walpole,⁴ who added 1.7 gm. of tyrosin, dissolved in sodium hydroxid, to 300 c.c. of broth and sterilized. They then infected this with a culture from human feces

TABLE 1.—SHOWING METHODS OF EXTRACTION USED, AND EFFECTS ON BLOOD-PRESSURE*

Specimen No.	Amount Used c.c.	Method	Extracts	Amount Extract, c.c.	Amount Extract Injected, c.c.	Effect on Blood-Pressure
1	2,500	Bain	Ether and Amyl	6	2	None
2	2,500	Bain	Ether and Amyl	6	3	None
3	2,500	Bain	Ether and Amyl	6	4	None
4	2,500	Bain	Ether and Amyl	6	5	None
5	2,500	Bain	Ether and Amyl	6	6	None
6	1,000	Abelous (first)	Alcohol	10	10	None
7	1,000	Abelous (second)	Ether	10	10	None
8	1,000	Abelous (first)	Alcohol	10	10	None
9	1,000	Abelous (second)	Ether	10	10	None

*The specimens of urine were normal and the source was the personnel of the laboratory.

and allowed it to putrefy at 37 C. for four days, together with the same quantity of broth with no tyrosin added, as a control. By extraction, a substance was obtained from the former which resembled parahydroxyphenylethylamine in its physiological effects.

The next question presenting itself is, If these bases are formed in the intestine, what are their effects in the organism? Are they absorbed as such in amount sufficient to cause symptoms, and do they remain as such in their circulation through the body, finally to be excreted unchanged in the urine? Some light has been thrown on this by the work of Ewins and Laidlaw,¹¹ who fed parahydroxyphenylethylamine to dogs (0.5 gm. to an 8 kilo dog) and were able to recover from the urine but 25 per cent. of the parahydroxyphenylacetic acid which was theoretic-

10. Abelous: Jour. de physiol. et path. gén., 1909, xi, 34.

11. Ewins and Laidlaw: Jour. of Physiol. (Eng.), 1910, xli, 78.

cally possible. They then perfused the substance through a dog's liver, and after two hours no trace could be obtained, but 70 per cent. of the possible amount of parahydroxyphenylacetic acid was recovered, showing that the liver had the power to change the base in its circulation through it. By perfusion through the uterus, .008 gm. of crystalline oxyphenylacetic acid was obtained, which fact would tend to show that either the muscles of the uterus or those of the blood-vessels, were able to transform the amine into the corresponding acetic acid.

In order to attack these questions, certain preliminary work seemed necessary, and we decided to proceed along the following lines: (1) To confirm, if possible, the finding of these pressor substances in putrid meat and urine; (2) to ascertain the relative amounts of the bases in the urine of healthy individuals on different diets, and the amounts in various diseased conditions, and for facilitating the latter to devise, if possible, a method for estimating the quantities of these substances in the urine, which would be simple enough for use with a series of cases and not too elaborate for the clinical laboratory as ordinarily equipped.

We accordingly attempted to obtain the two bases from putrid meat, using the method of isolation employed by Bayer and Walpole, which, briefly, is as follows:

One kilo of meat (beef) was stripped of its tendon and fat, ground up, transferred to a large bottle fitted with a perforated cork, with tube to allow the escape of gases, and placed in an incubator at 37 C. to putrefy. The meat was not inoculated with any organisms. After eight days when the mass had partially liquefied, it was removed and made acid with dilute HCl, and the proteins coagulated in a steamer at 100 C. The mass was then filtered and the filtrate evaporated in vacuum to a thick syrupy consistency. This was then thoroughly mixed with sand and extracted with acetone; the acetone solution was evaporated and the residue shaken with chloroform. The chloroform solution was extracted by means of dilute aqueous HCl, which was then made alkaline with dilute NaOH and extracted repeatedly with ether. By dehydrating the ethereal solution with anhydrous sodium sulphate and adding an anhydrous ethereal solution of oxalic acid, a white precipitate occurred, which was collected on a filter, dried and dissolved in distilled water or physiological salt solution. This represented the alleged ether-soluble principle, isoamylamine. The alkaline residue left after the ether extraction was washed with amyl alcohol to remove all other bases, the aqueous solution then made slightly acid with dilute HCl, and again alkalinized with sodium carbonate and extracted with amyl alcohol twice. In this manner the base parahydroxyphenylethylamine should be separated, dissolved in the amyl alcohol. The alcohol was now removed by distillation and the residue dissolved in distilled water for injection.

We were enabled thus to obtain two solutions which had the effects on blood-pressure ascribed to them by Dale and Dixon, namely, a rise, with the added observation that when given in large amounts they caused an immediate fall in pressure, the animal taking three or four deep inspirations, followed by an immediate cessation of respiration and heart-beat.

We then attempted to obtain from the urine such a pressor substance according to the method employed by Abelous. He first used an alcoholic extract, evaporating 1,000 c.c. of urine on the water-bath almost to dryness and taking up the residue with 500 c.c. of 95 per cent. alcohol. After standing and filtration, the alcohol was evaporated on the water-bath and the remaining liquid made slightly alkaline with sodium bicarbonate and injected into dogs in doses of 10 c.c. Abelous later, in

TABLE 2.—SHOWING EFFECTS ON BLOOD-PRESSURE OF URINARY EXTRACTS FROM PATIENTS ON VARIOUS DIETS AND IN VARIOUS ABNORMAL CONDITIONS

Specimen No.	Name	Condition of Patient	Am't Urine 24 hrs., c.c.	Amount Used, c.c.	Condition of Urine	Reaction	Diet	Extracts*	Amount Injected, c.c.	Effect on Blood-Pressure
10	Mrs. M.	Pernic. Anemia	1,200	1,000	Normal	Acid	Meat Free	Ether	3	None
11	Mr. K.	Gastric Ulcer	3,000	1,000	Normal	Acid	Beef, Eggs and Cereals	Amyl	3	None
12	Mrs. D.	Neurasthenia	1,100	1,000	Normal	Acid	Mixed	Ether	2	None
13.	Mr. H.	Gastric Ulcer	1,500	1,000	Normal	Acid	Mixed	Amyl	3	None
14.	Mrs. S.	Leukemia	1,700	1,000	Normal	Acid	Mixed	Ether	5	None
								Amyl	3	None
								Amyl	2	None
15	Mr. K.	Gastric Ulcer	2,200	2,000	Normal	Acid	Beef, Eggs and Cereals	Ether	4	None
16	Mr. L.	Arthritis	2,500	1,000	Normal	Acid	Mixed	Amyl	5	None
								Ether	3	None
17	Mr. L.	Arthritis	2,200	1,000	Normal	Acid	Mixed	Amyl	4	None
								Ether	2	None
18	Mr. L.	Arthritis	2,650	1,000	Normal	Acid	Mixed	Amyl	2	None
								Ether	3	None
19	Mr. L.	Arthritis	2,650	1,000	Normal	Acid	Mixed	Amyl	3	None
20	Mr. W.	Cystitis	?	1,000	Bacteria, Pus Cells	Alk.	Mixed	Ether	4	None
								Amyl	4	Fall, Urine stood in Lab. 4 days
21	Mr. L.	Tabes	?	1,800	Bacteria, Pus Cells	Alk.	Largely Meat	Ether	3	None
								Amyl	3	None
22	Mr. W.	Arthritis	2,250	1,000	Normal	Acid	Mixed	Ether	5	None
								Amyl	5	None
23	Mr. W.	Tabes	2,250	1,300	Bacteria, Pus Cells	Alk.	Largely Meat	Ether	4	None
								Amyl	4	None
24	Mr. B.	Cirrhosis	2,000	1,500	Normal	Acid	Mixed	Ether	4	None
								Amyl	4	None

*The amount of extract in each instance was 6 c.c., and the method was the author's modification of Abelous' and Bain's methods.

order to obtain a purer extract, modified the method as follows: 1,000 c.c. of normal urine was saturated with HgCl_2 , let stand for some hours and filtered. The mercury was removed with H_2S and the filtrate evaporated on the water-bath to about 12 c.c. This was taken up with 300 c.c. of absolute alcohol, shaken and filtered. The filtrate was evaporated until no more alcohol remained; the residue was now made alkaline with bicarbonate of soda and at the end with a solution of soda

and extracted several times with ether. To the ethereal solution was added a solution of oxalic acid in ether, which produced a white precipitate: this was dried on a filter over sulphuric acid, dissolved in 10 c.c. of distilled water and used for injection. We followed literally both of the above methods, so far as the none too exact description of Abeloos permitted, using the saphenous vein of dogs for injection, but were unable to obtain a rise of blood-pressure in several trials.

Attention was then turned to the method employed by Bain. He first extracted the urine directly with ether after rendering it alkaline to litmus. Then making it acid with HCl and again alkaline with sodium carbonate, he extracted with amyl alcohol; but later in order to avoid certain colloid substances which interfered with the ether extraction, he found the following method to be preferable and it was used by us:

Urine to the amount of 2,500 c.c. from persons on a mixed diet was thoroughly shaken with 4.5 per cent. of blood charcoal, which, he states, removes not only the colloid substances but the bases as well. This was filtered and the bases removed from the charcoal by boiling with dilute HCl. This mass was again filtered, the acid filtrate rendered alkaline with NaOH, and extracted ten times with ether. It was then made acid with HCl and alkaline with sodium carbonate and extracted with amyl alcohol twice. Both the ether and amyl alcohol extracts were then shaken with dilute HCl and the acid solutions evaporated almost to dryness on the water-bath. The excess of acid was removed in a desiccator over soda-lime, and the residue made neutral and taken up in 6 c.c. of distilled water. Two to 3 c.c. of this solution was used for each injection.

Although we extracted some ten specimens of urine by this method, in none of them were we able to obtain any pressor substance in either the ether or the amyl alcohol extracts.

In order to obviate any loss of substance which might occur during the extraction of large bulks of urine, we somewhat modified the previous methods of extraction, using from 1,000 to 2,000 c.c. of urine, which we evaporated in vacuum at 40 C. to about 75 c.c. In some instances 25 per cent. phosphoric acid was added in quantity sufficient to prevent any volatile amines going over; in others the acid was not used. The residue was taken up with 300 c.c. of absolute alcohol, filtered and the filtrate evaporated until all the alcohol had passed off. The solution was then made alkaline with NaOH and extracted with ether, the method of Bain being followed from this point. In none of ten urines did we obtain a pressor substance by this method.

As the urines in the first series were obtained from the personnel of the laboratory, and the others from hospital patients on a mixed diet, we sought to explain our inability to get any of the characteristic bases on the ground that perhaps there had not been enough meat in the diets. Accordingly, we placed in the hospital a young man 24 years of age, who was normal in every particular, so far as could be judged from physical examination and laboratory findings, and gave him a diet consisting

largely of meat. During this time he was constipated by administrations of opium. A specimen of his urine before the meat diet was started was extracted and extracts made from daily twenty-four-hour specimens following. On the fifth day a cathartic was administered, and the patient put on a meat-free diet, the urine being collected and extracts made as

TABLE 3.—SHOWING EFFECT ON BLOOD-PRESSURE OF URINARY EXTRACTS FROM A NORMAL INDIVIDUAL ON A MEAT AND MEAT-FREE DIET

Days	No. Urine	Am't Urine 24 Hrs., c.c.	Am't Urine Used, c.c.	Condition of Urine	Reaction of Urine	Method of Extraction	Extracts Made	Amount of Extract, c.c.	Am't of Ex- tract In- jected, c.c.	Effect on Blood- Pressure	Diet
1	24	1,600	1,000	Some phosphates, otherwise normal Normal	Acid	Our Modified	Ether Amyl	6 6	4 4	0 0	Mixed
2	25	1,600	1,000		Acid	Our Modified	Ether Amyl	6 6	4 4	0 0	
3	26	2,400	2,200	Normal	Acid	Our Modified	Ether Amyl	6 6	4 4	0 0	In 24 hrs. 4 gm. meat, egg s, cle soup, crea vegetables
4	27	1,750	1,000	Normal	Acid	Abelous'	Ether	10	8	0	
5	28	2,550	1,500	Normal	Acid	Bain	Ether Amyl	6 6	4 4	0 0	In 24 hrs. 4 gm. meat, egg s, cle soup, crea vegetables
6	29	1,950	1,000	Normal	Acid	Our Modified	Ether Amyl	6 6	4 4	Very slight rise 0	
7*	30	2,050	1,100	Normal	Acid	Our Modified	Amyl Ether	6 6	4 4	0 0	Meat-Fre
8*	31	2,100	1,000	Normal	Acid	Our Modified	Ether Amyl	6 6	4 4	0 0	
9	32	2,000	1,200	Normal	Acid	Our Modified	Ether Amyl	6 6	4 4	0 0	Meat-Fre

*Extracts of two days added together.

before. In one sample the method of extraction employed by Bain was used; in another Abelous' method, while in the rest our modification of Bain's and Abelous' methods was employed. As will be seen by the accompanying table (Table 3), in only one instance was there any rise of blood-pressure obtained by injections in dogs, and that so small as to be without significance.

TABLE 4.—SHOWING THE AMOUNTS OF AMINO SUBSTANCE IN THE URINE AND URINARY EXTRACTS UNDER VARIOUS CONDITIONS AND ON DIFFERENT DIETS, AS MEASURED BY THE REXCHESE-MALEATHI FORMALIN-TITRATION METHOD

No. Urine	Condition of Patient	24 hr. Urine, c.c.	Diet	Formalin Titration on Urine		Formalin-Titration on Ex-tracts				Amount of Urine Extracted c.c.	Action on Blood-Pressure		
				C.c. N/10 NaOH for 1,000 c.c. Urine	Gms. in Terms NH ₃ 1,000 c.c.	Gms. NH ₃	Ether Extract	Amyl Extract	C.c. N/10 NaOH			C.c. N/10 NaOH	Gms. NH ₃
10	Pernic. Anemia	1,200	Meat-Free	205	.369	.0005	.3	3.6	.006	1,000	0		
11	Gastric Ulcer	3,000	Beef, Eggs and Cereals	124	.222	.002	1.32	12.5	.022	1,000	0		
12	Neurasthenia	1,100	Mixed	265	.477	16.8	.030	1,000	0		
13	Gastric Ulcer	1,500	Mixed	40	.072	22.0	.039	1,000	0		
14	Leukemia	1,700	Mixed	112	.200	.002	1.2	7.1	.012	1,000	0		
15	Gastric Ulcer	2,200	Beef, Eggs and Cereals	178	.320	.019	11.0	11.0	.019	2,000	0		
16	Arthritis	2,500	Mixed	540	.972	.0	.0	3.95	.007	1,000	0		
17	Arthritis	2,200	Mixed	206	.370	.002	1.2	5.9	.010	1,000	0		
18	Arthritis	2,650	Mixed	180	.324	8.7	.015	1,000	0		
19	Arthritis	2,650	Mixed	210	.378	3.6	.006	1,000	0		
20	Cystitis	1,200 (?)	Mixed	4,580	8.24	.001	.6	16.6	.029	Alkaline Urine	0		
21	Arthritis	2,250	Mixed	120	.216	.001	.8	4.0	.007	1,000	0		
22	Tubes	?	Mixed	1,240	2.23	.0005	.3	16.1	.028	Alkaline	0		
24	Normal	1,600	Mixed	560	1.00	.013	7.4	15.	.027	1,000	0		
25	Normal	1,600	Mixed	520	.93	.013	7.4	12.6	.022	1,000	0		
26	Normal	2,400	Meat	220	.396	.009	5.1	20.7	.037	2,200	0		
27	Normal	1,750	Meat	240	.432	.010	6.0	12.0	.021	1,000	0		
28	Normal	2,550	Meat	200	.360	.001	0.6	3.9	.007	1,500	0		
29	Normal	1,950	Meat	280	.504	.015	8.5	15.	.027	1,000	Slight Rise		
30	Normal	2,050	Meat-Free	200	.360	.009	5.4	20.4	.036	1,000	0		
31	Normal	2,100	Meat-Free	170	.306	.009	5.4	20.4	.036	1,000	0		

In all the above experiments small dogs of about 6 kilos weight have been used in the physiological tests, the animals etherized, trachea exposed and cannula attached to ether bottle inserted, blood-pressure taken from the carotid and recorded on the revolving drum. In some instances the cord was cut in the cervical region and respiration kept up artificially.

We have extracted some thirty-seven urines for these pressor substances, and with none of our preparations has any such rise of pressure as described by Abelous and Bain occurred. There are several ways in which these negative results might be interpreted. (1) The substances are not in the urine, or (2) they occur in such small quantities as to be negligible in the amount of urine used for extraction, or (3) the technic on our part has been faulty. As we have gone over every step carefully in the methods employed, varying at times some detail where it occurred to us a mistake might be possible on account of the inaccuracy of the methods as given, it is hard for us to draw this last conclusion. It is possible, however, that results of different kinds might be obtained if one had to rely exclusively on the extraction methods as given by the various authors in their reported articles, for not only are they difficult to interpret, but woefully lacking in details which are essential to careful work. In considering whether these pressor bases are present in normal urine, as the work of Abelous and Bain would tend to show, it should be recalled, that we are starting out with the assumption that the substances are formed in the intestine and excreted as such in the urine. Consequently we should consider the question as to whether these bases, even if present in the bowel, may not be changed in the organism during their circulation through it, into compounds which, when excreted in the urine, may fail to give a pressor effect. The results obtained by Ewins and Laidlaw by perfusing parahydroxyphenylethylamine through various organs, as reported above, would tend to show that such is the case.

As to the third possibility, it is recognized by all who have attempted to isolate these bases from the urine, that they occur in extremely small quantities. Indeed, Barger and Walpole⁴ evaporated some 30 liters of urine and were unable to get enough of a pressor substance to identify it chemically. Again, the methods of extraction employed are not only tedious, so far as practical purposes are concerned, but somewhat uncertain, as it is a well-known fact that there are many ether soluble bases in urine, and from the lack of means of identification at hand we are unable to state the composition of a given extract. It occurred to us at the start that animal injection, for an estimation of different degrees of blood-pressure in different extracts, is faulty. For not only do the conditions affecting each animal at the time of injection have to be taken into consideration, but also the size of the animal and the number of injections into each; because in using two or more extracts on the same animal, the second probably would not give so great a rise as the first, even though it

contained a pressor substance in greater amount, on account of fatigue and other factors. Consequently the present methods did not seem to us suited for clinical work, assuming, as we did, that such pressor bases are present in the urine, since we required a more rapid and accurate means of estimation in order to carry out any further work. Reasoning along these lines, it was suggested by Dr. Woodyatt that the Rönchese-Malfatti¹² formalin titration for total amino and ammonia nitrogen might serve as an available means, as already applied by Henriques and Sörenson¹³ for a variety of purposes. We found that .005 gm. of tyramine (which corresponds closely physiologically and chemically to parahydroxyphenylethylamine) gave with this test a titration figure of 0.3 c.c. (N/10) NaOH. We accordingly tested by this method several specimens of urine before extraction and also the extracts from these same specimens, which supposedly contained the pressor bases. The technic employed was as follows:

A specified amount of the urine or extract was put in a small flask or beaker and diluted with 50 c.c. of distilled water. In a second container was put 5 c.c. of formalin (40 per cent. formaldehyd) with 10 c.c. of distilled water. To each of these solutions was added 3 drops of phenolphthalein. They were then treated with N/10 NaOH until the first permanent pink color appeared. The solutions were now added one to another, the pink color disappearing. The combined solution was then titrated with N/10 NaOH until the first permanent pink appeared and the reading was taken. The number of c.c. of N/10 NaOH required for this was used empirically as a comparative index for the total amount of ammonia and amino-nitrogen present in the urinary extracts. For instance, if it required 6 c.c. of N/10 NaOH to bring the pink color to the combined solutions in one extract and 8 c.c. in another, we figured that there would be more basic N substance in the latter and that animal injection might show a correspondingly great increase in blood-pressure, and that thus eventually we might for clinical purposes obviate the necessity of the physiological test. As a further comparison we multiplied the number of c.c. (say 6) empirically by .0018 which would give .0108 as the number of grams of titrable base in terms of NH_3 in 5 c.c. of urine or extract. In 100 c.c. there would be .2160 gms. and the amount for 1,000 c.c. of urine, or more, may readily be estimated from this percentage.

Although the results obtained by the use of the above method were by no means constant, we had in almost every case some formalin titrable substance. We therefore submit a table, showing the amount present in the various urines, and also the amount in the extracts of each urine in terms of N/10 NaOH, reckoned for 1,000 c.c. of urine, as that was the amount used for most of our extractions. We offer this merely as an interesting possibility. Furthermore, we had intended to check up and compare the results obtained by this method with those obtained by animal injection, but since we were unable to obtain in any of the urines a pressor substance which could be demonstrated by the latter means, no comparison was, of course, possible.

We hope soon to report some further work on the presence of pressor bases in the feces.

12. Hoppe Seyler: *Ztschr. f. physiol. Chem.*, 1909, lxi, 6, 499.

13. Henriques and Sörenson: *Ztschr. f. physiol. Chem.*, 1909, lxi, No. 1, 27.

CONCLUSIONS

1. Two pressor substances, corresponding to isoamylamine and parahydroxyphenylethylamine (as identified by Barger and Walpole), may be isolated from putrid meat.

2. The formation of these substances in the intestine, by bacterial putrefaction of proteins, is probable, but whether they are absorbed and remain unchanged in the organism to be excreted as such in the urine, is problematical.

3. The isolation of certain pressor substances from normal urine, as reported by Abelous and Bain, could not be confirmed by us.

4. Further, there is no definite chemical proof that these urinary pressor substances are isoamylamine and parahydroxyphenylethylamine.

5. Further work on the presence of these pressor bases in the organism, and their possible relation to certain cases of high blood-pressure, would seem highly desirable. For this purpose some practical means for the identification and measurement of these substances must be developed. The formalin-titration method, applied to suitably prepared urinary extracts, offers an interesting possibility in this connection.

I desire to express my extreme appreciation to Dr. Joseph L. Miller for the instigation of this work and for his valuable assistance at all times during the course of it; to Dr. S. A. Matthews for his aid in the physiological experiments, and to Dr. H. Gideon Wells and Dr. Rollin T. Woodyatt for suggestions and help.

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A CRITICISM OF TWO PERCUSSION METHODS FOR THE DIAGNOSIS OF THE ENLARGED THYMUS*

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Bednar (1852), Vogel (1856), von Mayr (1862) described briefly the percussion signs of the enlarged thymus. Sahli¹ (1882) first made an extensive study of these signs on living subjects. Blumenreich² (1902) investigated the signs on dead subjects, comparing the shape of the percussion dulness with the exposed portion of the gland as revealed at the subsequent autopsies. The principles for determining the thymus by percussion, as laid down by Sahli and modified and amplified by Blumenreich, hold to-day. They have the confirmation of anatomical fact. There have been advanced, however, two percussion methods for the recognition of the enlarged thymus which rest on anatomical hypotheses. The present paper is a discussion of the anatomical conditions underlying these two methods.

While the methods of Sahli and Blumenreich are directed at the more exact determination of the outline of percussion dulness, the methods in question — those of Jacobi³ and Boggs⁴ — aim at the determination of a movable dulness at the thymus site. Jacobi and Boggs' methods, then, are based on the hypothesis that the thymus is a movable organ.

The theory of the mobility of the thymus is not new. It had had advocates at least since the time when Grawitz (1888) became the exponent of the mechanical theory of thymic asthma. Some of the adherents to this theory of thymic asthma (Rehn⁵) have explained the dyspnea on the ground that during expiration the movable thymus was pushed up into the neck, during inspiration sucked back into the thorax against the trachea, obstructing it in a valvelike manner. Other exponents of this theory have held that owing to the connection of the thymus to the thyroid, the thymus may be drawn upward into the narrow outlet of the thorax by dorsal flexion of the head (the hypothesis of Boggs' percussion

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1. Sahli, Hermann: *Die topographische Percussion im Kindesalter*, J. Dalph. Bern, 1882.

2. v. Blumenreich, Robert: *Ueber die Thymus-Dämpfung*, Virchows Arch. f. path. Anat., 1900, clx, 35.

3. Jacobi, Abraham: In *Modern Clinical Medicine*, edited by Abraham Jacobi, D. Appleton & Co., New York, p. 37. *Diseases of Children* (Footnote).

4. Boggs, T. R.: *Percussion Signs of Persistent or Enlarged Thymus*, THE ARCHIVES INT. MED., 1911, viii, 659.

5. Rehn, L.: *Die Thymusstenose und der Thymustod*, Arch. f. klin. Chir., 1906, lxxx, 468; Cited by Gebelli, Beitr. z. klin. Chir., 1910, lxx, 20.

method) and, there becoming wedged, swells and exerts pressure. During their operations for the relief of thymic asthma, Rehn, Erhardt, Alsberg and others have seen the thymus bulge into the neck in expiration and disappear into the thorax in inspiration; and lastly, Rehn has watched the up and down movements of the thymus in the thorax by means of the fluoroscope. Jacobi and Boggs alone, so far as we know, have based a method of thymus diagnosis on thymus mobility.

Their respective methods hypothecate different movements of the thymus. While that of Jacobi presupposes a movement in an antero-posterior direction, away from and back against the anterior chest wall, the method of Boggs presupposes an up and down movement in the long direction of the sternum. For the diagnosis of the enlarged thymus, Jacobi⁶ places his subject on the back and percusses the normal thymus site for resonance, on the supposition that the enlarged thymus has fallen away from the anterior chest wall. Then, with his subject lying face downward, he percusses the same area from underneath for dullness, on the theory that the thymus has fallen back against the anterior chest wall. The change in the character of the percussion note coincident with this reversal in posture, Jacobi regards as characteristic of the thymus gland.

Boggs⁴ uses a more complicated procedure to determine the enlarged thymus. He puts his subject into the sitting position, depresses the chin toward the sternum and outlines the dullness "behind the manubrium and in the interspaces." He then retracts the head toward the midline of the back and repeats the percussion. If the former dullness is that of the thymus, it will now be found "to have shifted upward, often as much as an interspace or more."

Boggs explains the anatomical conditions underlying his method in these words:

The gland is attached by one or two suspensory or thyrothymal ligaments to the lower poles of the corresponding thyroid lobes. Otherwise the thymus is but slightly bound to the surrounding tissues and is free to move in the direction of the long axis of the sternum. If it is borne in mind that the thyroid gland is in turn connected to the hyoid bone and from this to the mandible by more or less continuous ligaments and muscles, it is seen that a ligamentous chain extends from the anterior part of the lower jaw obliquely downward and backward to the thymus.

Turning now to the consideration of this theory of thymus mobility, we may say at the outset that there are certain relations of the thymus to adjacent structures which force themselves on the attention of the operator in the course of an autopsy, because they obstruct his progress. When, for instance, the sternum is lifted up by its lower end and a view of the interior of the thorax obtained from underneath, it is necessarily

6. Jacobi, Abraham: *Therapeutics of Infancy and Childhood*. J. B. Lippincott Co., Philadelphia, Pa., 1908.

seen that a fascial attachment exists between sternum and thymus, because this attachment must be freed before the sternum can be removed. If an attempt is made to lift the thymus out of the thorax, the pericardium together with the heart and the diaphragm is lifted also. It is often difficult to locate the plane of cleavage between the thymus and the pericardium, so close is their union: and when in the separation of the two the left innominate vein is reached, it is often accidentally cut away with the thymus, so firmly adherent is it to the thymus. In order to become convinced of the truth of these statements, it is necessary merely to remove a thymus at autopsy.

The thymus is contained in a fascial sac, the capsule. Between the outer surface of the sac and the thymus a loose attachment exists. Surgeons⁷ (König, Rehn, Alsberg and others) in their operations for the relief of thymic asthma have made use of this fact, that when the capsule of the thymus is opened, a large part of the thoracic portion of the thymus can be drawn up into the neck. But between the outer surface of this sac and the thoracic structures a different condition exists. In front, the capsule is attached to the sternum loosely. At the sides, it is joined to the mediastinal pleura. Behind, it is bound to the pericardium so closely that it may be said to be united to that structure; it is entangled about the left innominate vein and closely joined to the sheaths of the great vessels. Fascial prolongations may connect it with the trachea, bronchi and pulmonary veins. Above, the sac is in continuity with the deep cervical fascia. It is important to note also in this connection that when the thymus is much enlarged the attachments of its capsule become more extensive. For example, in recorded cases in which the thymus has reached the diaphragm, the capsule has been found adherent there. While, then, the thymus may be regarded as loosely fastened inside its own capsule, the capsule itself must be thought of as most intimately attached, not to one thoracic structure alone, but to all thoracic structures. These attachments could not be more universal, nor those situated posteriorly much firmer, were they of an inflammatory origin. It is, therefore, difficult to regard the thymus as a movable organ.

The thymus, then, according to Boggs, is "attached" by "thyrothymal ligaments" to the thyroid, and is in a "ligamentous chain" connected with the "mandible." Since the thymus is in closer attachment to the pericardium than to the thyroid, and since the pericardium is in turn attached to the diaphragm, and the diaphragm to the liver, would it not be as reasonable to include the liver in this ligamentous chain attached to the mandible? Or, in reply to the argument that the thymus must be drawn up with the thyroid, since it is attached by thyrothymal ligaments to the

7. Holtz, Gerhard: Die Ursachen des Thymustodes. Beitr. z. Klin. Chir., 1907, IV, 509.

thyroid, would it not be as reasonable to say that this might occur, were not the liver present to weight the thymus down? The term ligament may be a proper term for the connections between the thymus and the thyroid, but the word gives to us an exaggerated impression of the actual condition. The connection between thymus and thyroid exists only in the deep cervical fascia, which is stronger about the trachea than elsewhere. Nor can we agree with Boggs in his statement that the thymus is not overlapped by the lungs, for the lateral and inferior parts of the thymus are always overlapped by the lungs. We have seen more than once a small thymus completely covered by the lungs. The description which Boggs gives of the anatomical conditions supporting his theory seem to us to convey a false impression.

For the same reasons we think that Jacobi's conception of thymus mobility in the anteroposterior direction is untenable.

We have investigated the truth of these methods in a series of twenty-nine autopsies performed at the New York Foundling Hospital. In each case a window was cut in the upper part of the manubrium; the pleura was not ruptured. The thymus could be inspected through this window. With the body in a dorsal position, we invariably found the thymus in close apposition to the sternal wall. It could not be pushed back easily. This finding is exactly opposed to Jacobi's theory. On performing Boggs' procedure exactly as performed by Boggs himself on the living subject, it was possible to observe that the thoracic portion of the thymus does not move. In some of the cases, by extreme retraction of the head, the upper, superficial parts of the thoracic portion of the thymus might be stretched upward a distance of 3 mm. But the middle parts remained essentially immobile. By exerting a powerful traction upward on the hyoid bone, the entire thymus could be pulled upward 2 or 3 mm., but it carried with it the diaphragm, pulling the costal margins in.

But even if the thymus were movable and could be drawn up, the lower border of thymus dulness would not be shifted upward, provided the lung margins remained fixed. Boggs evidently conceived of the thymus as hung, biblike, in *front* of the lungs, else how could he assume that the lower border of thymus dulness varies with the degree of elevation of the thymus? In reality the lower and lateral parts of the thymus lie *behind* and below the lung margins which, separated from each other above, meet at the level of the second or third rib, demarcating a V-shaped area of thymus tissue between them. This uncovered V-shaped area lies immediately behind the manubrium and represents the percussion area. The lower limit of the thymus dulness does not, therefore, coincide with the lower border of the thymus, but corresponds to the margins of the lungs. The idea that the lower border of thymus dulness rises when the thymus is drawn upward is actually no more reasonable than would be

the idea that the waistcoat opening would be shifted upward if the shirt is drawn upward by the neckband. It is true that a part of the shirt, previously below the level of the waistcoat opening, by this procedure would be raised above it and come into view. So, parts of the thymus previously below the level of the V-shaped opening formed by the lung margins would be drawn up into the percussion area, but the position of the lower border of thymus dulness would not be changed so long as the lung margins remained stationary.

How are the observations of Rehn, Alsberg and others, of the movements of the thymus occurring during their operations to be explained? Our answer to this question must be theoretical, for we have never seen the phenomenon described by them. We should suppose that the movement consisted chiefly in a suction of the cervical portion of an enlarged thymus into the thorax during inspiration, with its return during expiration — that such is the case rather than an expulsion of the thoracic portion of the thymus into the neck. Since in obstructive dyspnea some of the movable structures of the neck are pulled down toward the cavity of the thorax, among them the trachea with the thyroid, it could be conceived that the cervical part of the thymus capsule might also be carried down into the thorax. This appears to have been actually so in a case reported by Rehn. As a matter of fact, it is comparatively easy at autopsy, by catching the thoracic portion of the thymus with the forceps, to draw down the cervical portion into the thorax. It may also be that the thymus can be displaced inside its own capsule, stretched from one end of it to the other by the changes in intrathoracic pressure. In violent dyspnea the thoracic organs as a whole may to an extent rise and fall with the movements of the diaphragm.

If the methods of Jacobi and Boggs cannot be explained on the basis of a movable thymus, how may they be explained otherwise? The variables in the upper thorax are the lungs. We know that Boggs' procedure may increase the anteroposterior dimensions of the thorax at the level of the manubrium. To compensate for a loss of space somewhere else the lung margins may be forced further upward over the thymus. If this advance of the lung margins upward occurred as the result of Boggs' maneuver it would explain his "shift of the thymus dulness" upward.

Our conclusion, then, from an anatomic study of autopsy cases is that percussion methods of the thymus, based on the theory of thymus mobility, are founded on a false anatomical hypothesis.

PELLAGRA IN ILLINOIS

CONDENSED REPORT OF ILLINOIS PELLAGRA COMMISSION

(Concluded from page 168)

CASE G.—*Pellagra in a Man Suffering from Senile Dementia. Death in Three Months without Symptoms of Central Neuritis.*

History.—A. J. B., white male, farmer, 66 years of age. Nothing is known of his previous history. He was admitted to the Peoria State Hospital from the Soldier's Home at Quincy, Illinois, Nov. 1, 1910. At that time he was obese and somewhat feeble, with exaggerated knee-jerks but flexor plantar reflexes. Mentally he showed complete loss of memory for recent events, was irritable and peevish. Considered to be suffering from senile dementia.

In June, 1911, he was found to have a well-marked pellagrous eruption on the hands, with some desquamation. From this time he rapidly lost flesh and became more and more dull, although the specific symptoms of pellagra disappeared, and he died without any definite symptoms so far as can be discovered of central neuritis, Sept. 11, 1911.

At the autopsy evidences of healed tuberculosis in the lungs were found and the liver was described as being much engorged, its appearance suggesting almost a nutmeg condition, but its weight was only 44 ounces. The heart was thin and flabby and no definite changes were noted in the kidneys.

MICROSCOPIC EXAMINATION

Liver. Microscopically the liver shows slight increase in the amount of fibrous tissue, the capillaries are engorged, especially near the intralobular veins and there are small scattered islets of small-celled infiltration in the portal canals. Fatty degeneration is extremely marked, involving the outer layer of cells of each lobule and ceasing a little less than half way to the central vein. With osmic acid all the lobules are clearly marked out by the black stain.

Kidneys: The kidneys show marked increase of fibrous tissue and a few small subcapsular cysts. The vessel walls are thickened and in many places show hyaline changes. Small hemorrhages are present in some glomeruli. In the medullary rays many of the tubules appear to have undergone a hyaline change and to be completely occluded. This material suggests a lardaceous change but it does not show the characteristic staining reactions.

The suprarenals show marked fatty degeneration especially in the zona reticularis where every cell contains large fat droplets. Fatty changes are present but less marked in the fasciculata and still less so in the glomerulosa. Small hemorrhages are present in all layers and the central veins are engorged with blood.

The *pancreas* shows moderate increase of fibrous tissue and a few small hemorrhages.

Nervous System: In the nervous system the changes are extreme. Similar chromatolysis involving especially the giant pyramidal cells of the precentral cortex to those found in the other cases, as well as fatty degeneration of a most widespread character, are present. But besides this there is a marked overgrowth of glia cells, especially the satellite and perivascular cells. The arteries are markedly thickened and in this case there is a very moderate degree of small-celled infiltration of the vessel sheaths, thus forming a decided contrast to the other case examined. Further study of this nervous system is needed before expressing any opinion on the findings, but it cannot be regarded as an uncomplicated case of pellagra.

N. B.—It should have been stated on page 147 that the work on Protozoa was performed by Captains Siler and Nichols.

CASE 7—Pellagra in a Man Suffering from Chronic Alcoholism. Right Hemiplegia with Paraphasia and Left Parapraxia. Later also Weakness of Left Side.

History.—C. C., white male, ice handler. The patient has been healthy but a heavy drinker for years. In September, 1910, at the age of 51 it was noticed that his memory was defective and he seemed dazed and confused. This was thought to be due to alcoholism and he was sent to the Peoria County Poor Farm. His apparently stupid condition continued until early in January, 1911, when he became irritable, noisy and seemed to be worried.

Examination.—He was admitted to the Peoria State Hospital January 25, 1911, when he was found to have arteriosclerosis, a slight right hemiplegia with exaggeration of reflexes on that side, paraphasia, and parapraxia of the left side.

In April, 1911, he developed pellagrous lesions of both hands with some diarrhea. At the same time he began to lose flesh. The eruption had disappeared by early June but he continued to fail in general health. At the beginning of June he became very weak and seemed to have had some further cerebral insult, the left side being said to be weakened. At this time the reflexes were markedly increased on both sides and there was a bilateral Babinski phenomenon. He continued to lose strength and weight rapidly and died July 30, 1911, without having had any convulsive phenomena.

Neeropsy.—The neeropsy was performed seventeen hours after death and showed as follows: Marked atrophy of the cortex, especially in the frontal regions, but no gross lesion even when sectioned after hardening. Dense adhesions obliterating the pleural and pericardial sacs, with chronic posterior mediastinitis. Hypertrophy of the left ventricle with atheroma of coronaries. Liver engorged with blood and firmer than normal. Spleen and other viscera engorged. Kidneys showed no definite changes. No ulceration found in the intestines.

MICROSCOPIC EXAMINATION

Liver: Microscopically the liver shows no thickening of the capsule but there is a small celled infiltration of circumscribed character here and there in the portal canals in places almost outlining a lobule. The capillaries are engorged, especially towards the central veins. Fatty degeneration is slight but where present is in the cells at the periphery of the lobules. It is less in amount than that of any of the cases so far studied, a careful search being necessary to find the areas in which it occurs.

Spleen: The spleen shows increase of fibrous tissue with small hemorrhages.

Intestines: Small intestine shows infiltration of the mucosa and submucosa with leukocytes and in places small hemorrhages.

Nervous System: The examination is as yet very incomplete but the following facts are noteworthy:

Nerve Cells: These have so far been studied with thionin staining only in the anterior regions of the brain. Chromatolysis of axonal type is very marked in the giant cells of the precentral region. Many of the larger pyramidal cells also show similar change. This process is more marked in the sections in the anterior portions of the precentral gyri where many of the smaller elements are also affected. Pigmentary degeneration of a fatty nature staining well with Scharlach is extremely wide-spread and involves many of the smaller cells as well as the larger ones.

Glia and Vessels: The glia nuclei are moderately increased, the satellite cells are quite numerous and there are often rows of nuclei along the walls of the vessels. The vessels themselves show considerable hyaline degeneration of the intima with hyperplasia of the adventitia. Scharlach staining shows that many of the cells in this position contain fat droplets. The perivascular spaces, however, are not infiltrated with lymphocytes or plasma cells and there is nothing in the picture to suggest a parasymphilitic condition.

CASE S.—*Unhappy Marriage with Poor Adjustment. Spells of Moping and Mutism. Intestinal Symptoms Shortly Followed by Manic Excitement, and Three or Four Weeks Later by Stomatitis and Pellagrous Dermatitis. Increasing Restlessness, Severe Diarrhea with Rapid Emaciation and Death in Two Months.*

D. S., white female, a housewife and baker by occupation, 42 years of age.

Family History.—Incomplete. The mother and her relatives are said to have been weakly and to have died young. No insanity known.

Personal History.—Nothing known of her earlier life. She was married in 1896 and has never been happy. According to her husband she was always shiftless and careless about her household duties and has been cranky, nervous and dissatisfied. The patient's relatives blame the husband for the discontent and general unhappiness. She is said to have been quarrelsome with her neighbors, inclined at times to mope and refuse to talk. There have been three children, two normal, while the third died at the age of three weeks. In 1909 the husband left her and states that she did not succeed with the business, owing to her shiftlessness.

She has always lived in Havana, Mason County, Ill., and has worked in the bakery business owned by her husband since marriage. There has never been any financial difficulty and the patient has always had plenty to eat.

Present Illness.—In January, 1911, the patient began to suffer with gastrointestinal disturbance. About the middle of April she is said to have become "maniacal." At the beginning of May a sore throat developed, the tongue and gums being very red, and at the same time her hands became discolored and "bruised," due as was thought to the use of mechanical restraint.

She was admitted to the Peoria State Hospital June 2, 1911, when she presented marked coppery pigmentation with roughness and scaly desquamation of the skin of the dorsum of the hands and forearms, extending upwards to the junction of the middle and upper thirds. This area showed a well-marked line of demarcation and was entirely symmetrical on the two sides. The skin over the knuckles was rough and heaped up but without fissures. The tongue was reddened and denuded at the tip and there was severe diarrhea with loose, offensive stools.

Examination.—The examination was rendered unsatisfactory by the extreme restlessness of the patient. She was constantly talking, clapping her hands and singing, showing marked distractibility, with sound and motor speech associations. When alone she was constantly busy, tearing up her bed and bedding, jumping out of bed, showing all the appearances of a happy excitement. The excitement was readily increased by the presence of others and in answer to question she said she "felt fine," "I am an angel." Her "husband was extremely rich," had a "white automobile with gold trimmings," etc. No evidence of hallucinosis was obtained. Distractibility rendered orientation impossible.

Physical examination was incomplete but the knee-jerks were found to be exaggerated and it was suggested that the pupils did not react well, but there were no other facts on which to base any diagnosis of general paralysis of the insane.

The extreme restlessness continued with but little sleep. Diarrhea persisted and emaciation and exhaustion were progressive. Death occurred July 8, about two months after the onset of the first symptoms.

Permission for a post-mortem examination was refused.

IV. ANIMAL EXPERIMENTATION

Much time has been devoted to the attempt to transmit pellagra to lower animals. On the advice of the late Dr. Howard T. Ricketts, rhesus monkeys have been used in the main. All results have been entirely

negative, so that it will suffice to summarize the experiments which have been performed.

1. Twelve monkeys have been inoculated either subcutaneously or intraperitoneally with *defibrinated blood* obtained from patients suffering from pellagra in the recent or subsiding stage. (In one of these the case was probably not pellagra.)

2. Three monkeys have been injected subcutaneously with the filtrate obtained by passing the blood of pellagrins through Pasteur or Berkefeld filters.

3. Two monkeys were given hypodermic injections of the *blood serum* obtained from human pellagrins. Of these one was first filtered through a Berkefeld filter.

4. Three monkeys received injections of *cerebrospinal fluid* obtained from pellagrins. Of these one was procured post mortem and given subcutaneously, in the other two the fluid was drawn during life, one being injected into the subcutaneous tissues and the other into the peritoneal cavity.

5. One monkey has received subcutaneous injections of an *emulsion of spleen* obtained from a human pellagrin.

6. Four monkeys have been *fed for long periods on a strict corn diet*, and of these one has also received extremely mouldy corn meal, while one has been fed with a bacillus (Strain 67), obtained from the stools of pellagrins showing certain agglutinating relations with pellagrous blood-serum, and more fully detailed above.

7. One monkey has been fed with extremely moldy corn meal together with bacillus No. 67.

8. One monkey and one guinea-pig were inoculated subcutaneously with bacillus No. 67.

9. Twenty-three guinea-pigs were inoculated or fed with extracts from moldy corn meal.

10. One monkey and one guinea-pig were inoculated with a bacillus isolated from the blood of a human pellagrin.

11. One kitten received per rectum an emulsion of a stool from a pellagrin containing numerous living amebas.

12. Three monkeys have been fed with the fecal matter of pellagrins containing living amebas.

At this point it would be well to call attention to a physiological condition occurring in rhesus monkeys which does not appear to be generally known. During early life the skin of the perineum is white or bluish-white, but on reaching puberty these animals develop a vivid red color in this region similar to that which is well known in the closely related species of baboon. This erythema varies in degree from time to time and seems to bear some relation to the menstrual functions. When

at its height it is accompanied by marked edema and involves not only the perineum, but also the genital folds, extending sometimes upwards to the lower part of the abdomen, downwards on the inner surfaces of the thighs and around the anus to the root of the tail.

By a curious coincidence a number of our monkeys developed this erythema, as indicated in our preliminary report, at a more or less definite interval after they had been inoculated, and we were consequently inclined to attach some significance to its occurrence. The condition is very much more marked in the female than in the male, but we have seen some examples in the latter which were very distinct. Apparently one of the main reasons for its occurrence not being more generally known is that the animals, in captivity, frequently die before reaching maturity.

V. COMPLEMENT FIXATION EXPERIMENTS

This work was carried out by Dr. J. Frank Waugh and is briefly abstracted by him as follows:

The technic of the test was that described by Noguchi. An alcoholic extract of the liver from a pellagrin and a similar extract of the liver from a monkey which was killed forty-one days after the appearance of the erythema referred to above, were used as antigens.

Fifty-two sera from pellagrins which were tested with an alcoholic extract of human pellagra liver as antigen resulted as follows: thirty-four, or 65 $\frac{1}{3}$ per cent., gave a mildly positive reaction; twenty-eight, or 54 $\frac{1}{3}$ per cent., were negative. Five normal sera from persons who came in daily contact with the pellagrous patients proved to be negative, with the exception of one that was mildly positive. Thirteen specimens of blood from cases other than pellagra were used as controls. Among these were four sera from luetic patients, one of which gave a mildly positive reaction.

Fourteen sera from pellagrins were tested with monkey-liver antigen. Six gave a positive reaction, eight being negative.

Both antigens were used on eighteen sera from monkeys. Seven of the eighteen monkeys had been inoculated with blood from well-marked cases of pellagra. Four of the sera gave a positive reaction with both antigens, while three were negative. Four of the specimens were from animals having a well-marked perineal erythema, but which had not been inoculated. With human antigen, none was positive; with monkey antigen, two were positive and two negative. Seven of the specimens were from monkeys considered normal. One gave a positive reaction with both antigens, while six were negative.

Inhibition to hemolysis was only partial in all the positive cases. In no instance was there a strong reaction such as we get in lues when a luetic liver extract is used as antigen.

While the results of these tests are strongly suggestive, further work will be necessary to demonstrate whether or not a specific reaction is present.

VI. CUTANEOUS ANAPHYLACTIC TESTS WITH CORN EXTRACTS

This work was carried out by Arthur D. Hirschfelder, M.D., Baltimore, whose complete report follows:

The zeistic history of pellagra, as enunciated by Lombroso and v. Babes,⁵ that "Pellagra is to be considered as a chronic and periodically occurrent intoxication, which is due to a specific substance formed in more or less spoiled corn," is founded more on statistical evidence than on clear-cut experiments. Lombroso and subsequent workers, it is true, have isolated from corn toxic products which have some action on the nervous system of dogs, and v. Babes and Manicatide claim to have prevented this action in rabbits by injection of blood serum from a cured pellagrin. On the other hand, comparatively little has been done to test the sensitiveness of pellagra patients themselves to substances derived from corn.

If the zeistic theories of pellagra were correct, it seemed possible that the chronic corn intoxication presupposed by Lombroso and v. Babes might be accompanied by a condition of anaphylactic hypersensitiveness to products derived from corn, or perhaps only from spoiled corn. The present series of observations was undertaken, accordingly, with a view to determining the presence or absence of such sensibility.

Since, v. Pirquet⁶ has demonstrated that the cutaneous reaction affords the most delicate means of testing anaphylactic sensitization in man to tuberculin and other substances. Quite recently, Rufus Cole and W. S. Thayer were able to demonstrate hypersensitization to buckwheat infusion in a case of fagopyrismus reported by H. L. Smith.⁷ They found that if a drop of buckwheat extract were rubbed into a portion of the skin from which the epidermis had been removed by scratching, an urticarial wheal and general constitutional symptoms appeared within half an hour.

Since certain analogies between pellagra in man and fagopyrismus in animals had been recognized for decades, it seemed possible that a similar anaphylaxis to corn products might be met with in pellagrins. It seemed possible also that such a reaction, if positive, might be of importance for the diagnosis of pellagra.

In these observations, cutaneous tests were made with substantially the same technic employed by v. Pirquet, except that corn extracts were substituted for tuberculin in making the test.

5. Lombroso, C.: *Die Lehre von der Pellagra. Aetiologische, klinische, und prophylaktische Untersuchungen.* Transl. by H. Kurella, Berl., 1898; v. Babes, V., and Sion, V.: *Die Pellagra.* Nothnagel's Handb. d. spez. Path. u. Therap. Wien, 1901.

6. v. Pirquet, C.: *Tuberkulindiagnose durch cutane Impfung.* Berl. klin. Wehnschr., 1907.

7. Smith, H. L.: Buckwheat Poisoning, with Report of a Case in Man. *THE ARCHIVES INT. MED.*, 1909, iii, 350.

The procedure was as follows: 20 gm. of corn was extracted with 50 c.c. of ether, alcohol, 10 per cent. NaCl, or 0.2 per cent. NaOH. The extract was filtered and 1/10 vol. 5 per cent. carbolic acid added to the clear filtrate, so as to give it a content of 0.5 per cent. carbolic acid. The ethereal extracts were allowed to evaporate at 46 C., until the odor of ether had disappeared.

The site chosen for the test was an area on the patient's wrist which was subject to pellagrous pigmentation, thickening or desquamation, and, in the most cases, was bare, so as to be exposed to the action of light. A drop of the extract to be tested was placed on the skin and a pinhead area of epidermis beneath the drop was excoriated by the torsion of a v. Pirquet stylet. Into this excoriated area the extract was rubbed with a glass rod. A series of epidermal punctures were made in this way in a line across the wrist, with another line of duplicate punctures above them. In each series there were a pair of controls, in which only the pure NaCl or NaOH solution or alcohol was placed on the skin.

Within half an hour after the puncture, a small red or sometimes blanched areola, and occasionally a small papule, formed about the site of inoculation, but in only one case did these exceed 5 mm. in size, and no differences could be noted between the areas about the punctures with corn extracts and the controls. The reactions in sites which were nearest the middle of the forearm were often slightly more marked (areolas about 1 mm. larger than the rest), but these reactions were always quite as marked with the control fluids as with the extracts, and hence were of little significance.

The reactions, which were regarded as negative in all cases, consisting of simple traumatic reactions, were watched for about half an hour, and the sites of inoculation were again inspected three hours, twenty-four hours and forty-eight hours later, as well as at frequent intervals between.

Extracts were made from samples of good corn, spoiled corn taken from the Arkansas Insane Asylum at the time of a pellagra outbreak, and a sample of spoiled corn containing *Aspergillus fumigatus*. The extracts of the latter were filtered through a Berkefeld filter in order to avoid the danger of inoculating the aspergillus. Other extracts were made from the apparently excellent corn meal used at the Peoria State Hospital for the Insane at the time that pellagra was breaking out throughout the asylum, and when a number of cases of acute pellagra were developing. Tests were made on thirteen cases of well-defined pellagra diagnosed by Dr. George A. Zeller and confirmed by Drs. Singer and MacNeal of the Illinois Pellagra Commission.

These reactions were all negative. Just before leaving Peoria, a sample of spoiled corn was obtained which had been rejected by the asylum and sent out to the hog farm over a year previously. Extracts of

this corn were inoculated into six patients with subacute pellagra. The effects were observed for three hours after inoculation, but were uniformly negative.

In order to determine whether the presence of antibodies formed in a previous attack of pellagra might cause the reaction to be given by persons who had been afflicted with the disease in the previous year, but who were free from symptoms at the time of inoculation, observations were made on seven such patients. In all cases the results were negative.

The results of these tests, therefore, render it improbable that pellagra is due to or accompanied by a condition of hypersensitiveness of the individual to products derived from good or from spoiled corn.

I take pleasure in expressing my thanks to Dr. George A. Zeller and the Illinois Pellagra Commission for placing at my disposal the patients and laboratory of the Peoria State Hospital, as well as to Dr. Carl Alsberg of the Bureau of Plant Industry for furnishing samples of good and spoiled corn.

VII. DIETARY STUDIES

In view of the alleged relations between pellagra and deficiency in food both as regards quantity and quality the following points have been submitted to study:

1. The nutritive value of the general diet supplied to the inmates of the Peoria State Hospital, the institution where the largest number of cases of pellagra developed.

2. A rough estimate of the relative amounts of meat used in the different state hospitals in comparison with the prevalence of pellagra.

3. The quality of corn in use at the state hospitals and elsewhere. In connection with this experiments have been made to determine the toxicity of some samples of moldy corn.

4. A comparison of the effects of an excessive corn diet with one which was free, or practically so, from maize products. An analysis of the excessive corn diet has been carried out and a rough comparative estimate of the nutritive value of the corn-free diet used in this experiment was also made. It was unfortunately impossible under existing conditions to make this estimation more complete.

1. For the study of the general diet at the Peoria State Hospital a group of representative patients, about fifty-three in number, was selected. The quantities of food which they actually consumed during a period of seven days were accurately determined by weighing the total food served and food left uneaten. Representative samples of the food used were taken and analyzed for protein, fat, carbohydrates, mineral matter and phosphorus. The energy values were calculated. The results of this study are summarized in Table 14. As far as possible the samples were composited. Thus, the samples designated animal foods represent foods chiefly of animal origin, i. e., meats and cheese; vegetable food, foods chiefly of vegetable origin, i. e., fruits, cereals, potatoes and other vegetables; bread, breads, cake, etc.; mixed foods, food containing appreciable

TABLE 14.—SUMMARY OF GENERAL DIET

	Weight of Food Used.	Protein		Carbohydrates		Fat (Ether Extract)		Fuel	Ash (Mineral Matter)		Phosphorus	
		Per cent.	Quantity, gms.	Per cent.	Quantity, gms.	Per cent.	Quantity, gms.		Per Cent.	Quantity, gms.	Per cent.	Quantity, gms.
20,039 Animal foods	58.53	13.99	8,188.35	3.59	2,101.23	12.33	7,216.75	2.12	1,240.84	0.162	94.82
20,040 Vegetable foods	374.81	1.87	7,008.95	16.26	60,944.11	0.37	1,386.80	1.09	4,085.43	0.041	153.67
20,041 Bread	134.17	8.49	11,391.03	57.40	77,013.58	0.63	845.27	1.19	1,596.62	0.095	127.46
20,042 Mixed foods	77.31	1.96	1,515.28	15.11	11,681.54	1.42	1,097.80	0.97	749.91	0.036	27.83
20,043 Coffee and tea	294.36	0.04	117.74	0.99	2,914.16	0.03	88.31	0.06	176.62
20,044 Milk	24.07	3.12	750.98	4.96	1,193.87	2.56	616.19	0.74	178.12	0.094	22.63
20,045 Butterine	12.48	0.44	54.91	88.21	11,008.61	3.30	411.84	0.014	1.75
20,047 Syrup	26.44	0.16	42.30	76.17	20,139.35	0.07	18.51	1.25	330.50	0.007	1.85
20,050 Salt	0.65	99.75	648.37
Total in food used	29,069.54	175,987.84	22,278.24	9,418.25	430.01
20,048 Waste food	34.15	3.18	1,085.97	19.62	6,700.23	2.73	932.30	1.37	467.86	0.064	21.86
20,049 Waste food	19.71	3.48	685.91	21.77	4,290.87	3.24	638.60	1.64	323.24	0.047	9.26
Total in waste food	1,771.88	10,991.10	1,570.90	791.10	31.12
Amount actually consumed ¹	27,297.66	164,996.74	20,707.34	8,627.15	398.89
Average per man per day	73.51	444.34	55.77	23.23	1.07
Average per kilo body weight ²	1.10	6.62	0.83	0.35	0.016

1. Net amount for 7 days, 53 1/21 subjects.

2. Average weight of subjects, 67.1 kilos.

quantities of both vegetable and animal materials, i. e., puddings. The other samples consisted of the materials their names indicate. By waste food is meant the food left on the tables and plates, which was in such condition that it could not be separated. This was collected and analyzed and its nutritive values deducted from those of the total food used in computing the quantities of food and nutrients actually consumed.

The distribution of the nutrients among animal and vegetable foods has been calculated and is summarized in Table 15. Such classification, however, is not absolute, for the samples were taken from cooked foods which contain materials derived from both sources. Nevertheless, the figures probably represent the true character of the diet.

TABLE 15.—DISTRIBUTION OF

Laboratory No.	Food Materials	Fresh Food			Dry Substance			Protein		
		Quan- tity kilos	Per cent. of Total	Per Man per Day gms.	Quan- tity kilos	Per cent. of Total	Per Man per Day gms.	Quan- tity gms.	Per cent. of Total	Per Man per Day gms.
20,039	Animal foods.....	58.53	5.84	18.75	7.92	8,188.35	28.17
20,044	Milk.....	24.07	2.40	2.74	1.16	750.98	2.58
Total animal foods.....		82.60	8.24	222.44	21.49	0.08	57.86	8,939.33	30.75	24.07
20,040	Vegetable foods.....	374.81	37.38	73.42	31.30	7,008.95	24.11
20,041	Bread.....	134.17	13.38	90.85	38.39	11,391.03	39.19
20,043	Coffee and tea.....	294.36	29.35	3.30	1.39	117.74	0.40
20,047	Syrup.....	26.44	2.64	20.53	8.68	42.30	0.15
Total vegetable foods.....		829.78	82.75	2,234.61	188.10	79.49	506.56	18,560.02	63.85	49.98
20,042	Mixed foods.....	77.31	7.71	15.04	6.36	1,515.28	5.21
20,045	Butterine.....	12.48	1.24	11.34	4.79	54.91	0.19
Total mixed foods.....		89.79	8.95	241.81	26.38	11.15	71.06	1,570.19	5.40	4.23
20,050	Salt.....	0.65	0.06	1.75	0.65	0.27	1.75
Total food used.....		1,002.82	100.00	2,700.62	236.62	100.00	637.22	29,069.54	100.00	78.28
20,049	Waste food.....	53.86	5.37	145.05	15.12	6.39	40.73	1,771.88	6.10	4.77
Amount actually consumed...		948.96	94.63	2,555.57	221.50	93.61	596.49	27,297.66	93.90	73.51

2. When the work of this commission was planned it was hoped that it would be possible to study the general diet at each hospital in the same manner as that actually carried out at the Peoria State Hospital. This, however, has unfortunately been found to be impossible owing to lack of time and assistance. The findings at Peoria detailed in the last section revealed deficiency in the amount of animal protein served to each patient. Since the main source of this constituent was provided in the meat it was thought that a comparison of the meat supplied to each institution

daily per capita might afford some sort of basis for conclusions as to the quantity of animal protein at the other hospitals. In Table 16 is shown the average daily amount of meat in ounces supplied to each individual including both patients and employees.

In considering these figures it must be remembered that the weights represent almost entirely uncooked and undressed meats. Secondly, the employees, while being absolutely fewer in numbers, receive relatively much larger amounts of meat. It would be quite impossible to determine exactly what the relative proportion is, and since the proportion of employees to patients is approximately the same in the different institutions it is quite permissible to make comparisons on the figures as they

NUTRIENTS—GENERAL DIET

Carbohydrates			Fat			Fuel Value		Ash			Phosphorus		
Quantity gms.	Per cent. of Total	Per Man per Day gms.	Quantity gms.	Per cent. of Total	Per Man per Day gms.	Per cent. of Total	Per Man per Day Calor's	Quantity gms.	Per cent. of Total	Per Man per Day gms.	Quantity gms.	Per cent. of Total	Per Man per Day gms.
2,101.23	1.19	7,216.75	32.39	1,240.84	13.17	94.82	22.05	0.26
1,193.87	0.68	616.19	2.77	178.12	1.89	22.63	5.26	0.06
3,295.10	1.87	8.87	7,832.94	35.16	21.09	11.63	319	1,418.96	15.06	3.82	117.45	27.31	0.32
60,944.11	34.63	1,386.80	6.22	4,085.43	43.37	153.67	35.74	0.41
77,013.58	43.76	845.27	3.79	1,596.62	16.95	127.46	29.64	0.34
2,914.16	1.66	88.31	0.40	176.62	1.87
20,139.35	11.44	18.51	0.08	330.50	3.51	1.85	0.43	0.01
161,011.20	91.49	433.61	2,338.89	10.49	6.30	72.58	1,991	6,189.17	65.71	16.67	282.98	65.81	0.76
11,681.54	6.64	1,097.80	4.93	749.91	7.96	27.83	6.47	0.07
.....	11,008.61	49.41	411.84	4.37	1.75	0.41	0.01
11,681.54	6.64	31.46	12,106.41	54.34	32.60	15.79	433	1,161.75	12.33	3.13	29.58	6.88	0.08
.....	648.37	6.88	1.75
175,987.84	100.00	473.94	22,278.24	100.00	60.00	100.00	2,743	9,418.25	100.00	25.36	430.01	100.00	1.16
10,991.10	6.25	29.60	1,570.90	7.05	4.23	6.38	175	791.10	8.40	2.13	31.12	7.24	0.08
164,996.74	93.75	444.34	20,707.34	92.95	55.77	93.62	2,568	8,627.15	91.60	23.23	398.89	92.76	1.07

stand. It will be noted that there is a big increase in the Peoria figures between the first three years and the fourth. In part this was due to an actual increase in the amount of meat supplied to each patient, but it is also in part to be explained by the fact that during this period many of the attendants who used to live off the grounds of the hospital have been required to take up their residence within the institution.

The actual analysis of the food at the Peoria State Hospital was made during the fourth period, July, 1910. to July, 1911, so that this figure.

S.2. must be used as a basis of comparison. From the results of the analysis we are forced to conclude that the animal protein constituent of the dietary provided at all the state hospitals, with the possible exception of that at Jacksonville, is certainly small.

The period of observation has been too short and the data are obviously too incomplete to justify any conclusions. It may, however, be noted that the number of cases of pellagra has diminished at Peoria and Dunning coincidently with increased meat supply, whereas they have apparently increased at Elgin with diminished meat. This may be a matter of pure coincidence, but is worthy of further investigation.

TABLE 16.—AVERAGE DAILY AMOUNT OF MEAT IN OUNCES SUPPLIED TO EACH INDIVIDUAL, INCLUDING BOTH PATIENTS AND EMPLOYEES

	July, 1907 to July, 1908	July, 1908 to July, 1909	July, 1909 to July, 1910	July, 1910 to July, 1911	Average
Peoria	5.3	5.8	5.9	8.2	6.3
Anna	11.3	10.9	10.6	9.8	10.65
Chester	6.4	5.0	4.5	6.4	5.6
Elgin	7.1	7.7	6.9	5.9	6.9
Jacksonville ..	10.6	10.9	11.3	10.5	10.8
Kankakee	8.7	7.8	8.0	8.2	8.2
Watertown	8.2	7.9	8.4	8.3	8.2
Dunning	6.5	6.5	6.6	7.5	6.8

3. Samples of corn meal from eight institutions were analyzed chemically for moisture and acidity. For comparison similar determinations were made on nineteen other samples of corn meal from various sources. The results are shown in Table 17. The acidity has been calculated on a moisture-free basis and is expressed in terms of N/10 NaOH solution required to neutralize the alcoholic extract of 100 grams of meal.

The official standard in this country requires that "maize meal, corn meal or Indian corn contain not more than 14 per cent. of moisture." An Austrian investigator states that sound corn and corn meal should require less than 30 c.c.—generally 15 to 25 c.c.—N/10 NaOH solution to neutralize the alcoholic extract of 100 grams of the meal.

Judged by the moisture content, acidity, presence of molds and other microorganisms, and the presence of insects, the corn meal used in the state institutions is, on an average, of very good grade. It was found to be of better quality than the corn meal purchased in the open market in Urbana and in Alabama, and also better than six samples from Italy. Cultures were made from all parts of the samples for molds. No quantitative determination of the molds present was attempted. Of all samples only one, No. 20006, obtained from Anna, contained no molds. Both

moisture and acidity of this sample were the lowest of all the twenty-seven samples examined.

The changes brought about by the action of molds on corn meal were studied with special reference to the formation of toxic substances.

For this purpose portions of corn meal were sterilized and inoculated from pure cultures of molds. After a good growth had been secured, the moldy meal was extracted with 90 per cent. alcohol for three to four hours at a temperature of 65 to 70 C. The alcohol extract was filtered off (using the centrifuge when necessary) and evaporated *in vacuo* over sulphuric acid to dryness. The dried residue was next extracted with absolute alcohol and the extract filtered. This filtrate was likewise evaporated to dryness *in vacuo* over sulphuric acid. The residue thus obtained was extracted with water, the water solution made alkaline with sodium carbonate and extracted with ether. The ether solution was allowed to evaporate spontaneously. As this is essentially the Stas-Otto method for the extraction of ptomains, the residue from the ether extract should contain the toxic substances originally present. Other residues and fractions were also tested, however, and in those cases in which toxic products were found it was in fractions other than the last residue described.

TABLE 17.—AVERAGE ACIDITY AND MOISTURE CONTENT OF CORN MEAL FROM VARIOUS SOURCES

	Acidity, c.c. N/10 NaOH	Moisture Per Cent.
Corn meal from state institutions (8 samples)	40.7	13.99
Corn meal from local grocery store (3 samples)	51.3	12.58
Slightly spoiled meal from Kankakee (1 sample) (not used as food for patients)	60.3	15.69
Good meal from Alabama (3 samples)	65.1	11.74
Damaged meal from Italy (6 samples)	112.1	15.76
Damaged meal from Alabama (3 samples)	113.0	11.83
Very badly spoiled and moldy meal (3 samples)	174.7	65.06

Of the five molds (three varieties of *Penicillium*, one *Mucor* and one *Monascus purpureus*), only one, *Monascus purpureus*, gave a toxic substance when grown on corn meal in pure form.

Another sample of meal on which a blue green species of *Penicillium* had grown, but which had become contaminated by other organisms, was very toxic.

Some further experiments to investigate the presence of toxins in corn were carried out by Captains Nichols and Siler.

After taking some corn meal mush from a boiler just before it was served and letting it stand in a sterile Petri dish for two days, we found it covered with slimy, reddish growth, which proved to be that of *Bacillus mesentericus fuscus*. This organism and strains of *Penicillium glaucum*, *Aspergillus flavus* and *Diplodia* recovered from musty corn, which were

kindly furnished us by Professor Burrill of the University of Illinois, were used in trying to discover any evidence of toxins. Moist corn meal was put in large flasks, sterilized and inoculated with these organisms. After a rich growth was obtained, it was scraped off with some of the corn meal, diluted with water, thoroughly shaken, centrifuged or filtered and the clear liquid used for injection of rabbits and guinea-pigs. A large number of rabbits were used, and injections were given subcutaneously, intraperitoneally and intravenously. The results were uniformly negative. When corn-meal mush was allowed to decompose naturally and a similar extract used for injections, the animal died; but the result is readily attributable to putrefactive organisms. Feeding experiments with infected corn were started, but soon given up, as it was found that the animals refused to eat the corn after the first day and died of starvation.

4. *Feeding Experiments.*—At the suggestion of Captains Nichols and Siler, two cottages, with a capacity of about sixty patients, were filled with non-pellagrous patients of the chronic class. Careful stool examinations were made for protozoa. One cottage was then placed on a generous corn diet—approximately 16 ounces of corn food-stuffs per day. The other cottage, containing about sixty patients, was placed on a corn-free diet of the same general nature. These diets were continued for one year and the patients were placed directly in charge of Dr. Watkins of the hospital staff, who followed them with great care. Dr. Watkins' report included a description of the daily diet in each cottage. This detail may be seen in the complete report. In addition, a personal chart was kept for each patient, noting carefully the following points:

1. Examination of the feces.
2. Semi-monthly weights.
3. Mental conditions as to mania and stupor.
4. Physical conditions, with special attention to diarrhea, gastritis, stomatitis, and skin lesions.

This experiment was carried out during the entire year, and on September 15, 1910, these facts are noted: Nearly all the patients gained gradually on both wards from September to March or April, when they gradually fell off during the hot weather until they averaged about the same weight as on the same date the preceding year. On the corn diet twenty-five patients gained in weight during the year, twenty-nine lost and four remained unchanged. The average loss and gain on both cottages was from 2 to 3 pounds.

There were sixteen patients on the corn diet who suffered with diarrhea during the year, while only ten on the corn-free diet suffered from the same malady, and there were more cases of constipation on the corn-free diet cottage than on the corn diet cottage.

During the year, the corn diet cottage showed four cases of pellagra, with one death from the disease. The corn-free cottage showed five cases of pellagra, with two deaths from the disease. During the year there were four suspected cases of pellagra on the corn-free diet cottage.

Of the four suspected cases, the examination of the stools was negative as to active amebas, but in two cases there were encysted amebas and encysted flagellates. One patient had a mild erythema of the dorsum of the hands during January, 1910. This patient gained 7 pounds during the year and at present shows no symptoms of pellagra.

In a general way, the results of this experiment may be summarized as follows:

FEEDING EXPERIMENTS IN TWO COTTAGES. DURATION ONE YEAR

	Patients	Cases of Pellagra	Suspects
Corn diet cottage	59	4	1
Corn-free diet cottage	58	5	5

It is evident from these results that an extensive corn diet did not favor the production of pellagra. Cases developed in each ward in practically the same proportion, and this proportion agrees in general with that found throughout the institution, which was also on a corn-free diet. It is not claimed that this experiment absolutely disposes of all forms of the corn theory of the production of pellagra, but it is difficult to reconcile the results with the ordinary theories incriminating corn as a causative factor in the production of the disease.

The analysis of the corn diet was conducted similarly to that of the general diet with the exception that a separate sample was made of all foods derived from maize. The quantities of foods and nutrients consumed are summarized in Table 18, and the distribution of the nutrients among animal and vegetable foods in Table 19. There were fifty-six patients in this group.

No complete study of the corn-free diet was made, but the quantities of food consumed by the group taking this diet, fifty-seven in number, were determined for two days. These figures are given in Table 20.

Before any definite conclusions can be drawn from such studies as this it is obviously necessary that further investigations be made with accurate metabolism experiments. It is difficult to judge of the adequacy of the protein content in the above studies because very little information

TABLE 18.—SUMMARY. CORN DIET

Laboratory No.	Food Materials	Weight of Food Used, Kilos	Protein		Carbohydrates		Fat (Ether Extract)			Ash (Mineral Matter)		Phosphorus	
			Per Cent.	Quantity, gms.	Per Cent.	Quantity, gms.	Per Cent.	Quantity, gms.	Fuel Value, Calories	Per Cent.	Quantity, gms.	Per Cent.	Quantity, gms.
20,051	Animal foods	73.36	10.37	7,628.17	4.68	3,442.61	11.30	8,312.28	1.97	1,449.13	0.113	83.12
20,052	Vegetable foods	268.41	2.03	5,448.72	13.61	36,530.60	0.73	1,939.39	1.18	3,167.24	0.046	123.47
20,053	White bread, etc.	100.46	9.52	9,563.79	56.63	56,890.50	2.87	2,883.20	1.25	1,255.75	0.116	116.53
20,054	Mixed foods	86.08	1.94	1,669.95	14.44	12,420.95	0.69	593.95	0.65	559.52	0.032	27.55
20,055	Coffee and tea	475.19	0.03	142.56	1.32	6,272.51	0.02	95.04	0.05	237.60
20,056	Milk	89.07	3.10	2,761.17	4.87	4,337.71	2.67	2,378.17	0.71	632.40	0.093	82.84
20,057	Butterine	13.81	0.53	73.35	87.25	12,075.40	3.66	506.51	0.016	2.21
20,058	Corn foods	283.69	4.05	11,489.44	29.47	83,603.44	2.75	7,801.48	1.57	4,453.93	0.105	297.87
20,059	Syrup	10.72	0.16	17.15	76.00	8,147.20	0.05	5.36	1.05	112.56	0.006	0.61
20,061	Salt	0.35	99.77	349.20
Total in food used		38,794.30	211,654.52	36,104.27	12,723.87	731.23
20,060	Waste food	148.17	3.10	4,602.57	20.48	30,406.66	3.56	5,285.53	1.20	1,781.64	0.062	92.05
Amount actually consumed ¹		34,191.73	181,247.86	30,818.74	10,942.23	642.18
Average per man per day		87.22	462.37	78.62	2898	27.91	1.61
Average per kilo body weight ²		1.39	7.37	1.25	46.2	0.45	0.026

1. Not amount for seven days, fifty-six subjects.

2. Average body weight, 62.7 kilos.

is available regarding the food requirements of the insane. It is permissible, however, to make the following suggestions:

1. The protein content of the general diet is probably sufficient but is certainly not excessive.
2. This diet is chiefly vegetable in nature, much more so than the average American dietary. It is conceivable that a deficiency in animal protein may predispose to pellagra.
3. An excess of corn products in the dietary of fifty-seven patients continued for a period of one year did not result in the development of more pellagra than in a similar squad of fifty-seven patients whose diet contained no corn, other conditions being equal.
4. The quantities of nutrients, energy, and mineral substances ingested per man per day by the patients receiving the corn diet were adequate but not excessive. The scanty data at hand seem to show that the corn-free diet was at least equal in nutritive value to the corn diet.
5. The quality of corn meal supplied to the state hospitals is of high grade.
6. The growth of the commoner varieties of mold in pure culture on corn meal does not give rise to great toxicity.

VIII. SIMULIA IN ILLINOIS

Owing to the importance placed on the buffalo gnat as a possible carrier of the disease by Sambon, the Commission invited Prof. Stephen A. Forbes, State Entomologist, to make an investigation in this field. He very kindly consented, and presented an admirable report. It is only possible here to outline a part of his findings. The reader who is interested is respectfully requested to consult the monograph published by the commission for Professor Forbes' full report.

GENERAL DESCRIPTION

The buffalo gnats or black flies, all species of the genus *Simulium*, are small, two-winged insects with thick, hump-backed bodies and sharp piercing and sucking beaks. They vary in length, according to species, from $1/25$ to $1/6$ of an inch—1 to 4.5 mm. They are notorious for the immense numbers in which they swarm in early spring, especially along the larger streams, and for the painfulness of the punctures made by the females (the males being inoffensive), and the ferocity and fierceness of their attack. They are, generally speaking, more annoying than seriously injurious to mankind, although several deaths have been more or less plausibly attributed to their attack; but to domestic animals, especially to cattle, horses and mules, and even to poultry, they are a terrible and terrifying scourge.

As is very commonly the case with blood-sucking diptera, the young or larvæ of these flies are aquatic. The eggs are laid in patches on objects under water, the larvæ transform there to pupæ and the pupæ to winged adults, which escape to the surface each in a bubble of air absorbed from the water through the gills of the pupa and stored up under its cuticle.

The larvæ are so abundant locally, under the most favorable conditions, that the water is said sometimes fairly to boil as the winged insects burst from its surface, each in its air bubble.

NUMBER AND GENERAL DISTRIBUTION OF SPECIES

There are about sixty-five species of this genus in the world. Twenty-five of them have been found in North America and fifteen in the United States. Nine species are known by us to occur in Illinois, and a possible tenth species is represented by an unidentified larva found in Vermilion

TABLE 19.—DISTRIBUTION OF

Laboratory No.	Food Materials	Fresh Food			Dry Substance			Protein		
		Quan- tity Kilos	Per cent. of Total	Per Man per Day gms.	Quan- tity Kilos	Per cent. of Total	Per Man per Day gms.	Quan- tity gms.	Per cent. of Total	Per Man per Day gms.
20,051	Animal foods.....	73.56	5.25	20.83	6.96	7,628.17	19.66
20,056	Milk.....	89.07	6.36	10.11	3.38	2,761.17	7.12
Total animal foods.....		162.63	11.61	414.87	30.94	10.34	78.93	10,389.34	26.78	26.50
20,052	Vegetable foods.....	268.41	19.15	47.11	15.75	5,448.72	14.05
20,053	White bread, etc.....	100.46	7.17	70.59	23.60	9,563.79	24.65
20,055	Coffee and tea.....	475.19	33.91	6.75	2.26	142.56	0.37
20,059	Syrup.....	10.72	0.76	8.28	2.77	17.15	0.04
Total vegetable foods.....		854.78	60.99	2,180.56	132.73	44.37	338.60	15,172.22	39.11	38.43
20,054	Mixed foods.....	86.08	6.14	15.25	5.10	1,669.95	4.30
20,057	Butterine.....	13.84	0.99	12.51	4.18	79.35	0.19
20,058	Corn foods.....	283.69	20.24	107.35	35.89	11,489.44	29.62
Total mixed foods.....		383.61	27.37	978.60	135.11	45.17	344.67	13,232.74	34.11	33.76
20,061	Salt.....	0.35	0.02	0.89	0.35	0.17	0.89
Total food used.....		1,401.37	100.00	3,574.92	299.13	100.00	763.09	38,794.30	100.00	98.96
20,060	Waste food.....	148.47	10.59	378.75	42.08	14.07	107.33	4,602.57	11.86	11.74
Amount actually consumed...		1,252.90	89.41	3,196.17	257.05	85.93	655.75	34,191.73	88.14	87.22

County, Illinois, and also abundant in Yellowstone Park. One American species, *S. hirtipes*, found in northern Illinois, occurs in Europe; and another, *S. reptans*, abundant throughout Europe, is reported from Greenland also, but not elsewhere in North America. It is to this latter species, indeed, that the spread of pellagra has been ascribed in Italy.

GENERAL FEATURES OF LIFE HISTORY OF ILLINOIS SPECIES

Neither the life histories nor the habits of any of our American species have been sufficiently studied, and the one best known (*S. pictipes*) happens to be of the least interest from our present point of view, since

it has never been known to bite. Our Illinois species differ considerably in distribution, life history and places of most frequent occurrence. Two of them—the so-called turkey gnat (*S. meridionale*) and the buffalo gnat (*S. pecuarum*) are the species to which southern accounts of these insects usually apply. Although they occur occasionally far to the north, they are southern in their general range and predominant numbers, and have not been found by us in northern Illinois. *S. venustum*, the black fly or sand-fly of the northern woods, is, on the other hand, perhaps the most abundant species in the north, although *S. vittatum* is frequently found

NUTRIENTS. CORN DIET

Carbohydrates			Fat			Fuel Value		Ash			Phosphorus		
Quan- tity gms.	Per cent. of Total	Per Man per Day gms.	Quan- tity gms.	Per cent. of Total	Per Man per Day gms.	Per cent. of Total	Per Man per Day Calories	Quan- tity gms.	Per cent. of Total	Per Man per Day gms.	Quan- tity gms.	Per cent. of Total	Per Man per Day gms.
3,442.61	1.63	8,312.28	23.02	1,449.13	11.39	83.12	11.32	0.21
4,337.71	2.05	2,378.17	6.59	632.40	4.97	82.84	11.28	0.21
7,780.32	3.68	19.84	10,690.45	29.61	27.27	12.68	428	2,081.53	16.36	5.31	165.96	22.60	0.42
36,530.60	17.26	1,959.39	5.43	3,167.24	24.89	123.47	16.82	0.31
56,890.50	26.88	2,883.20	7.90	1,255.75	9.87	116.53	15.87	0.30
6,272.51	2.96	95.04	0.26	237.60	1.87
8,147.20	3.85	5.36	0.01	112.56	0.88	0.64	0.09	0.00
107,840.81	50.95	275.10	4,942.99	13.69	12.61	40.50	1,367	4,773.15	37.51	12.18	240.64	32.78	0.61
12,429.95	5.87	593.95	1.65	559.52	4.40	27.55	3.75	0.07
.....	12,075.40	33.45	506.54	3.98	2.21	0.30	0.01
83,603.44	39.50	7,801.48	21.60	4,453.93	35.00	297.87	40.57	0.76
96,033.39	45.37	244.98	20,470.83	56.70	52.22	46.82	1,580	5,519.99	43.38	14.08	327.63	44.62	0.84
.....	349.20	2.75	0.89
211,654.52	100.00	539.94	36,104.27	100.00	92.10	100.00	3,375	12,723.87	100.00	32.46	734.23	100.00	1.87
30,406.66	14.37	77.57	5,385.53	14.64	13.48	14.13	477	1,781.64	14.00	4.55	92.05	12.54	0.23
181,247.86	85.63	462.37	30,818.74	85.36	78.62	85.87	2,898	10,942.23	86.00	27.91	642.18	87.46	1.64

in its company. The first of these is said by Prof. F. L. Washburn to be an annoyance to stock in Minnesota, and the second a torment to mankind. These two species are the commonest ones in northern and central Illinois. We have likewise a fifth species, hitherto undescribed, the larvæ of which are abundant in the Illinois river, and two or three others which occur more sparingly in various parts of the state.

Our species differ also in the number of generations, the two especially southern forms (*S. pecuarum* and *S. meridionale*) having so far as known but one generation in a year, which reaches the winged stage in early spring, while the two most abundant northern forms (*S. venustum* and

S. vittatum) appear in the winged stage at intervals throughout the summer, and evidently have two or more generations: just how many is not known. *S. pictipes* also develops at least two generations.

Some of these species breed mainly in small streams, while others find favorable situations for reproduction in the largest rivers. *S. meridionale* and *S. vittatum* are examples of the first habit, and *S. pecuarum* and *S. venustum* of the second. Larvæ and pupæ of all are limited to flowing streams, the larvæ quickly dying, indeed, if transferred to quiet water. They are evidently very sensitive to a deficiency of oxygen, and can live as a rule only where the current is swift or where its movement is so interrupted by shallows or by objects lying or growing or suspended in the stream as to produce at least a surface whirl or ripple.

TABLE 20.—COMPARISON OF CORN AND CORN-FREE DIETS. QUANTITIES OF FOOD USED, PER MAN, PER DAY, DURING THE FIRST TWO DAYS OF EXPERIMENTS

Kind of Food	Weights of Food Used per Man per Day (gms.)	
	Corn Diet.	Corn-Free Diet
Animal foods	289.73	301.23
Milk	336.52	352.98
Coffee and tea	1,046.25	1,099.56
Butterine	34.46	45.44
Other foods ¹	1,736.60	1,984.82
Total foods used	3,443.56	3,784.03
Waste foods	366.79	470.70
Amount actually consumed	3,076.77	3,313.33

1. Includes for:

Corn Diet	Gm.	Corn-Free Diet	Gm.
Vegetable foods	651.16	Vegetable foods	983.68
White bread, etc.	280.98	White bread, etc.	430.88
Mixed foods	169.46	Mixed foods	570.26
Corn foods	635.00		
Total	1,736.60	Total	1,984.82

The larvæ are rather peculiar creatures, with slender, cylindrical, maggot-like bodies, thickened and club-shaped at the hinder end, by which they adhere to some submerged object, and with a pair of fan-like clusters of filaments near the mouth. They are commonly grouped in colonies, often thickly covering the object to which they are attached. They spin from their mouths silken threads, with which they form a loose network covering the surfaces they occupy, and by means of which they can recover their position if swept away by the current. They move mainly like a measuring worm, with the aid of a sucker near each end of the body. They pupate in a case or nest composed of web spun from the

mouth, and the pupa breathes by a pair of tufted gills extending forward from the open mouth of the case.

In the two species whose life histories have been fairly well followed, namely *S. pictipes* and *S. venustum*, about two months elapse in summer between the laying of the egg and the appearance of the winged fly, the egg stage lasting about one week, the larval four weeks, and the pupal three. In colder weather the development proceeds more slowly. As these species hatch from the egg in New York in the first part of May, there is time, at this rate, for three successive generations, the last of which hibernates in the larval stage, pupating in April of the following year. We have sufficient data concerning the times of occurrence of the winged black flies in Illinois to bring all but three or four of our species under this category. The single-brooded species appear in the winged stage in central Illinois in April and May, the date of maximum abundance here in two successive years having been about April 25. The farther south one goes and the earlier the spring, the earlier is the swarming time of the gnats. Indeed, we have one report from Louisiana of the appearance of winged buffalo gnats during every month of an unusually mild winter, and a consequent failure of the usual spring rush in February and March. Although six of our Illinois species send out summer broods, these are so scanty and scattering that it is difficult to find winged specimens in the field, even by careful expert search, at any time except in spring.

BREEDING SITUATIONS OF THE BLACK FLIES

The number of our Illinois species, and the fact of their distribution in all parts of the state, make it practically certain that black flies may be found sooner or later wherever and whenever the somewhat peculiar local conditions required for their breeding are present. These conditions are, in the first place, running water continuous through the breeding season, and, in the second place, either a rippling surface or a fairly rapid flow of the stream. It is also necessary that there should be solid objects in the water, not more than a few inches under the surface, on which the eggs may be laid and to which the larvæ may cling. The water must also, of course, contain a sufficient supply of the smaller plankton and other organic particles on which the larvæ feed. As they remain attached like plants and cannot search for food, they are dependent on whatever chance brings within reach of the prehensile apparatus about the mouth. The species which breed in rivers find these conditions most general during high water, especially in spring. Then the current of the stream is comparatively swift and strong near the shores, and the marginal overflow reaches to trees and shrubs, stranded driftwood, and the like, which create the necessary surface disturbance and at the same time provide places of attachment for the eggs and larvæ. In the smaller

streams, on the other hand, times of flood are less favorable, except where there is a rocky bed; but as the summer grasses grow, dipping into the stream, and marginal shrubs droop their twigs loaded with leaves into the water, and as the heavier objects on the bottom of the creeks and rivulets are brought near the surface by the shrinking of the stream, many suitable places may be found here and there for the black fly to deposit eggs and for the young to reach the pupation stage.

Myriads of these insects are sacrificed, as our field notes show, when the waters fall, leaving the pupæ exposed and liable to dry out. Small fish and certain carnivorous insects, especially case worms, devour the larvæ, and their numbers in summer and fall are rarely very great in our latitude. The bottom lands of our principal rivers—the Illinois, the Mississippi, the Ohio and the Wabash—from the middle of April to the middle of May, are almost the only situations in which the black flies may be called a plague. As the swarms of these insects are readily blown about by the wind, they are often carried to considerable distances from their place of origin, and cases are on record in which they must have been borne several miles in this way. The adults are not long-lived, and an outbreak does not ordinarily continue annoying longer than ten days. A storm of wind and rain may, in fact, put an end to it in even less time.

The description of the various species found is necessarily omitted here.

POSSIBLE RELATION TO PELLAGRA

To ascertain definitely whether the distribution of black flies in Illinois and the times of their principal appearance, local and general, have any relation to the occurrence and frequency of cases of pellagra, would require a very much broader and closer survey of the state, with this point especially in mind, than it has been possible for me to make. With the exception of a part of the data obtained at Havana and Peoria in 1910, those here reported are the product of general miscellaneous collections made during many years, with no thought of any pathological application. They are sufficient, however, to show the common occurrence of black flies throughout the state. Our specimens have come from sixteen counties—five in northern Illinois, eight in central and three in southern, as follows: northern Illinois: McHenry, Carroll, Cook, La Salle and Mercer; central Illinois: Peoria, Tazewell, McLean, Vermilion, Champaign, Mason, Fulton and Green; and southern Illinois: Wabash, Saline and Jackson.

The places and situations of occurrence are such as to warrant the opinion that black flies might be found in larger or smaller number in every county of the state. They would be most abundant, of course, along the larger rivers (and it is only there that they become noticeable as

pests), and the species would differ with the size and character of the streams, and, to some extent, with the latitude.

The only attempt I have been able to make toward a comparison of local facts concerning simulium with the local data of pellagra is based on observations made at Bartonville, near Peoria, in the latter part of August, 1910. The location there of the general hospital for the insane, in which pellagra is almost continuously present, gave us reason to examine the surroundings of this institution as carefully as possible, and visits were made to this place by Mr. C. A. Hart on August 29, 30 and 31. In a small stream just north of the hospital grounds at Bartonville, which leaves the bluff on which the buildings stand, passes under the highway and flows eastward through low ground towards the river, simulium larvæ were obtained just below the wagon bridge, on the leaves of trailing branches and on other objects in the stream, although none could be found in this stream above the highway. The point at which the black flies were breeding was about a third of a mile in direct line from the hospital buildings. No pupæ were seen in the water and no winged flies could be caught by diligent sweeping of the vegetation in that vicinity. Two small streams emerging from shady valleys in the bluffs to the south of the hospital grounds were destitute of simulium larvæ.

In Kickapoo Creek, between Bartonville and Peoria, a very few larvæ and pupæ were found, and a considerable number were taken in favorable places all along Farm Creek near the East Peoria station, across the river from the hospital. These were not in the deeper or wider parts of the creek, but in its very smallest lateral divisions and the shallowest margins of the riffles. All the specimens taken at this time in these streams proved to be *Simulium vittatum*. A thorough search of the river margin at Peoria, made August 31, was without result, no trace of simulium being found in the main stream. Not a single winged black fly could be found here, although the presence of small numbers of the pupæ showed that a very few might be abroad. The probability of any activity of black flies in conveying pellagra at this place and time seems, consequently, very small.

I have next to scan my miscellaneous data with reference to the possibility of distinguishing successive generations, and periods of greatest abundance, of the insects on the wing. Throwing all these data together, I find that we have made collections of adults on thirty-six of the 204 days from April 3 to October 24, and that there are two rather conspicuous blanks in the series—one extending from May 22 to June 14, twenty-two days, and the other from July 21 to August 11, twenty days. Accepting these as indications of the dividing lines between successive generations, we may conclude provisionally that we have three generations

in the season, the first covering April and the greater part of May, the second the latter part of June and most of July, and the third extending from the middle of August to the last of October. These intervals might perhaps be filled in, at least in part, if we had larger collections; but they correspond fairly well to such definite facts as we have concerning the length of a generation period of *simulium*. Precise work on this subject has been done only in New York, and there only for two species, *S. pictipes* and *S. venustum*, the first of which possibly does not occur in Illinois. For both these New York species it has been shown that in the warmer part of the summer the development of a generation requires about eight weeks, one of which is passed in the egg, four in the larva and three in the pupa stage. Making reasonable allowance for a prolongation of the period of development of the earliest and latest generations grown in the cooler weather of the season, we may fairly suppose that we have three generations of six of our Illinois species, the first extending through April and May, the second coming in June and July and the third in August, September and October. Entomologists will readily understand that with any such succession of generations as this in a single season, the periods of the later ones are always the longer. The other three Illinois species seem to give us but one generation each, which we know to appear in April and May.

It has been a matter of special interest to me to compare this hypothetical scheme of generations with pellagra data communicated to me by Dr. H. Douglas Singer, in a letter written December 29, 1911. The statements of this letter are illustrated by a curve showing the number of fresh cases of pellagra occurring at the Bartonville General Hospital for each month from July, 1909, to September, 1911. There are five high points in this curve for these twenty-six months: one at the beginning of the record, which, starting with twenty-one cases for July, 1909, rises to seventy-one for August, and then drops rapidly away to three in December. This is much the highest wave of the curve. The next wave of increase begins with a single case in April, 1910, rises to sixteen cases in May and to thirty-four in June, and drops to four in July. We have next a lower wave of sixteen cases in August, 1910, fifteen in September and one in October. Two cases in the following March (1911) become four in April and six in May, fall to one in June, rise again to three in July and seven in August and fall to none in September.

On the supposition of a connection between black-fly outbreaks and pellagra waves, we should naturally expect the former to precede the latter somewhat; just how far, of course, no one can tell, since that would involve a knowledge of the incubation period of the disease. A comparison of my hypothetical periods of our black-fly generations with these waves of frequency of new cases of pellagra gives an indication of a correspondence between the two series for the first two generations

of the year, but negatives the idea of any stimulating influence of the implied third generation. Thus, omitting the 1909 record as begun too late to serve our purpose, the March and April generation of black flies for 1910 connects with an April and May increase of pellagra; the supposed June and July generation of that year with high numbers of new cases for August and September; the March and April generation of 1911 connects with an April and May increase of pellagra for that year, and the June and July generation with a July and August increase. The August to October generation, on the other hand, is followed by a decline in the number of new cases in both 1909 and 1910, the record for 1911 breaking off within this period.

These interpretations, it is true, are decidedly hypothetical, but they may be taken as at least suggestive of a causal relationship, and as indicative of a method of analysis which, used in proper cases, may give definite results. We need to know accurately the life histories of the various species of simulium for the entire year in some locality where pellagra is more or less prevalent, and to know also the exact facts as to the local abundance of the winged flies during the successive generation periods. If there are recognizable and considerable variations in abundance, or definite breaks in the insect series, correlated in a uniform way with waves of pellagra increase presently following; and if exceptions to this correlation are to be clearly explained by exceptional circumstances, we shall have strong reason to believe that one or more of the species of simulium then and there present are causally related to the conveyance of pellagra from one person to another. Other and more direct lines of operation on this problem belong to the pathologist rather than to the entomologist.

IX. GENERAL SUMMARY AND DISCUSSION

1. *Pellagra in Illinois.* A conservative estimate of the number of pellagrins in this state from July, 1909, when it was first recognized, to September, 1911, would be five hundred. The vast majority of these cases have occurred in the state and county hospitals for the insane, notably at the Peoria State Hospital. There has been a progressive diminution in the total numbers of new cases in the three years under consideration in these institutions. It is, however, becoming increasingly evident that there is a considerable number of cases outside the state hospitals, although we have no figures which will justify any statements as to the actual numbers. Two somewhat striking foci seem to exist in Chicago and Peoria, but it is probable that the disease is prevalent over wide areas.

2. *Clinical Manifestations and Pathology.*—Pellagra is a systemic disease characterized by a skin eruption, symptoms of gastro-intestinal disturbance and more or less well-marked general debility and emaciation. The only reliable diagnostic symptom is the skin eruption which begins

as a bright red erythema generally on the backs of the hands. This color becomes more copper-colored in the course of a few days with thickening of the epidermis, especially about the knuckles and often with fissures which bleed easily. In severe types bullæ form, which may rupture, and thus give rise to superficial ulcers. In the course of two or three weeks the color becomes gradually darker from increased pigment deposits and begins to desquamate. This stage lasts a variable time from a few weeks to several months, at the end of which the appearance is pink and delicate-looking, like that of an infant. Following this it gradually returns to a normal condition. The chief points in diagnosis are the course: the more or less absolute symmetry on the two sides of the body, the sharp line of demarcation from the healthy skin and the absence of marked itching and pain. The commonest sites are the backs of the hands and lower parts of the forearms, often extending as a cuff around the wrist just above the palm; the elbows and arcs on the inner sides of the arms and forearms; the forehead and cheeks; the neck, and finally the dorsa of the feet. At times the eruption is widespread over the whole body. Denudation and swelling of the tongue with sometimes ulceration, inflammation and even ulceration of the mucosa of the cheeks, gums and lips should probably be regarded as manifestations similar to the skin eruption. Excoriations about the anus and genitalia, with inflammation of the mucosa of the vagina are fairly common.

The gastro-intestinal symptoms are very frequent, but not always marked and may be absent. They consist of diarrhea with liquid putrescent stools of peculiar odor, which is thought by some to be characteristic. More or less anorexia is present as a rule, but sometimes appetite is excessive.

Emaciation and general weakness are present in a degree more or less corresponding with the severity of the gastro-intestinal symptoms.

Besides these features there is a great tendency to the development of mental disorder of delirious type and in the late stages to the occurrence of the central neuritis syndrome.

The *course* of the disease is extremely variable. In many cases it consists of annual exacerbations lasting one or two months with apparent recovery in the intervals. Some patients seem to have one attack and then to recover, at any rate without recurrence during one pellagrous season. The percentage of recurrences in individuals recovering from an attack in 1909 was 31.25 in 1910 and 13.24 in 1911. Of the 1910 attacks which did not prove fatal only 8.6 per cent. recurred in 1911.

Death may result in any attack whether the first or later recurrence. This may transpire during the acute phase apparently from general exhaustion, or at a later period, after all characteristic pellagrous lesions have disappeared, with symptoms of central neuritis. Pathologically one case dying during the acute stage presented lesions resembling those of

central neuritis, although the characteristic clinical syndrome was not observed during life. The mortality has been very high in this state, pellagra being given as the immediate cause of death in 49.6 per cent. of the 258 cases at the Peoria State Hospital. Of the 408 cases recorded, 189, or 46.3 per cent. are dead, although in some of these instances intercurrent disease seemed to be the actual cause.

Symptoms which appear to be of bad *prognostic import* are the early appearance and severe degree of gastro-intestinal and mouth symptoms, marked emaciation and the occurrence of nervous symptoms such as delirium and signs of central neuritis.

Treatment has seemed to have but little if any influence on the course of the disease. Arsenic has been used in various forms, but the cases so treated do not seem to have shown any more favorable outcome than those without it. We can recommend only general measures such as careful nursing and diet, the avoidance of exposure to the sun, which seems to aggravate the skin lesions, together with the copious administration of fluids, which may if necessary be given by hypodermoclysis.

Feces: The stools of pellagrins are exceedingly variable in character. In general, there is a marked diarrhea during the acute attack, with frequent watery evacuations, nearly always very foul-smelling. Later, the stools become less fluid and contain abundant mucus. Blood and epithelial cells are frequently observed in severe cases.

The numerical relationships of the normal forms of fecal bacteria are more or less disturbed and new forms of bacteria of several different kinds appear in the feces in appreciable numbers. Protozoa, especially amebas and flagellates, are frequently found.

Cultures of the fecal bacteria in the various stages of pellagra also indicate disturbances of the normal relationships of the intestinal bacteria. In addition to this, some forms of bacteria not ordinarily found in the feces of healthy men are found here in appreciable numbers.

There is some evidence indicating that some of these bacterial and protozoal forms play a part in producing some of the pathological changes observed in the cases of pellagra which we have studied. Whether any of them is a primary factor in the disease itself, or whether they are all secondary invaders with no essential causal relation to pellagra, cannot be decided from the evidence at hand. For those forms which have been studied more particularly by us the latter hypothesis seems to be the more probable. Nevertheless, these bacteria and protozoa seem to be worthy of further attention.

Blood: Moderate anemia is the rule with a color index which is frequently normal or even slightly above. Leukocytosis occurs occasionally in severe cases, but as a rule the number of white cells is within normal limits. There appears to be no characteristic change in the relative proportions of the different varieties of white cell.

No abnormalities are noticeable in the size, shape and staining properties of the red cells. No abnormal bodies have been found either in fresh or in stained specimens. Cultures have been almost all sterile.

Urine: Indican has been increased and there are variations in color, quantity, specific gravity and composition. A trace of albumin with hyaline casts are not uncommon.

Cerebrospinal fluid: This shows no increase of cell elements or albumin content and cultures have been uniformly sterile.

Complement fixation tests with the blood-serum of pellagrins as an amboceptor and extracts of pellagrous liver, tongue and spleen as antigen have given results which cannot be regarded as specific at present. Negatives with positive cases and positives with normal sera have been encountered too frequently to permit of any interpretation.

Anaphylactic tests by von Pirquet's method using extracts of healthy and damaged maize have proved uniformly negative.

The post-mortem findings are those of a generalized intoxication. Fatty degeneration of the liver with inflammation and ulceration of the intestinal mucosa and the occurrence of islets of subacute inflammatory exudate in the portal canals of the liver suggest an intoxication of intestinal origin which may be either primary or secondary. There is nothing characteristic of pellagra in the lesions found in the nervous system; they can only be regarded as evidence of an intoxication.

The chemical analysis of one pellagrous brain shows no deficiency in sulphur or phosphorus, but only a disturbance in the combinations of the former. This is quoted here only in relation to the possibility of a deficiency in certain elements in the diet which has been suggested as a cause for pellagra.

3. Animal Experimentation: Inoculations of monkeys and other animals with tissue emulsions and body fluids have been entirely unsuccessful.

Feeding with the dejecta of human pellagrins has given rise to no symptoms. Similar negative results were obtained from inoculation with organisms isolated from the stools.

Feeding experiments with maize both healthy and in a spoiled condition have been without result.

Injection of extracts from maize contaminated with five different molds was found to be toxic in one instance only, the organism being *Monascus purpureus*. Another sample containing a blue-green *Penicillium* and contaminated with bacteria was highly toxic.

4. Diet: Maize has formed but a small part of the hospital dietaries and the quality used has been excellent. Careful observations of a squad of individuals fed with a large excess of corn products for a period of

twelve months compared with a similar number given a strictly corn-free diet revealed no differences in the number of cases or the severity of pellagra which developed in both.

Detailed study of the general diet of the Peoria State Hospital reveals a deficiency in protein constituents and especially in animal protein. Comparisons between the average amount of meat supplied to the inmates of the Peoria and other state hospitals suggest a greater or less degree of deficiency in animal protein in all. It is also noticeable, although it may be quite accidental, that pellagra has diminished in Peoria and Dunning, coincidentally with an increase in meat supply, while at Elgin the number of pellagrins has increased with a decrease in the amount of meat provided *per capita*.

GENERAL DISCUSSION OF THEORIES AS TO ETIOLOGY

The various conceptions as to the etiology of pellagra have already been enumerated under the head of "Current Views on Pellagra," as the basis on which the work of this commission was planned. It is therefore only necessary here to discuss the bearing of the work accomplished on these different theories. This can with advantage be arranged under the same two main headings.

1. *In Relation to Maize.*—It may be said that all work directed to this question has uniformly yielded negative results. The evidence collected in this report all tends to discredit any such assumption, and while we fully appreciate that negative findings can never be accepted as positive proof for or against any given proposition, it nevertheless seems to us that the burden of proof must rest with the zeists. The following facts may be especially emphasized as tending to discredit any causal relations between maize and pellagra: (1) *Sound maize*: (a) Excessive corn feeding was not accompanied by more pellagra than was observed in individuals kept on a strictly corn-free diet, other conditions being, as far as possible, identical as regards the age, sex, mental and bodily condition, habits and occupation of the patients and the size, location and general arrangement of the buildings, although cases developed under both conditions; (b) maize products constituted only a moderate proportion of the general diet of those affected; (c) cutaneous tests in pellagrins with extracts of corn gave rise to no anaphylactic symptoms. (2) *Damaged maize*: (a) The corn used in the state institutions has been of high grade; (b) all experimental work has necessarily been performed on animals. In none has there been any pellagra-like manifestations, and, in fact, with few exceptions the toxicity has been low; (c) cutaneous anaphylaxis tests with extracts from damaged corn were negative.

If one adds to these direct observations the keen critical analysis by Sambon of the foundations on which the maize hypothesis rests, one cannot but feel that the arguments in its favor are extremely slender.

2. *Antizest Theories*.—As long ago as 1905 Sambon⁸ discussed the probability that pellagra was an infective disease, the causative agent of which was carried by some blood-sucking insect. His reasoning is based on analogies with other infections of that character. The main grounds are: (1) the seasonal recurrence; (2) the existence of endemic foci, while, apparently, the disease is not contagious; (3) the fact that recurrences occur in previously infected individuals even after they have been removed from the infected locality and such recurrences occur at the same seasons of the year.

All investigations carried out by us with the object of demonstrating the presence of a blood parasite have so far failed. Nevertheless, it is quite possible that a parasite may live and propagate in the blood, but require special methods for its demonstration, not yet discovered. The failure to produce pellagra in animals with such infected blood may well be the consequence of various reasons. For instance, it is quite possible that, as Sambon supposes, some second phase of existence in an intermediate host such as the biting insect, may be necessary. Again, the animals used for experimentation may not be susceptible. It is thus quite obvious that the negative findings so far enumerated cannot be accepted as entirely controverting this theory.

Post-mortem findings do suggest a possible nidus for the growth of an organism in the intestine, a suggestion which might be considered as especially plausible from the clinical picture. Nevertheless, it must always be remembered that the infection of the intestinal tract may be secondary to, and not causative of, pellagra. We have studied the fecal flora with especial care and do not consider that our findings justify us in making any claim for them as primary causal factors.

The relation of simulia to pellagra, hypothesized by Sambon, finds but little support from the researches we have been able to make. The particular variety, *S. reptans*, which he claims to be of world-wide distribution, is said by Professor Forbes to be unknown in North America as yet except in Greenland.

Quite recently, and therefore not included in the statistical studies, we have had the opportunity to observe two cases, both apparently first attacks, in which pellagra developed during the winter months following several weeks of intensely cold weather. One of these arose at the Kankakee State Hospital, the first symptoms being observed Dec. 24, 1911. This patient had been an inmate of the hospital more than a year and had shown no previous signs of pellagra. The attack was very severe and ended fatally. The second case developed Dec. 31, 1911, at the Jacksonville State Hospital. This man had also been in the hospital for over a year. Professor Forbes informs us that the latest date on which adult simulia have been captured in Illinois is Oct. 24. It would there-

8. Brit. Med. Jour., 1905, ii, 1272.

fore be necessary to concede an extremely long incubation period in order to explain these cases on the theory that the *causa morbi* is borne by these insects.

PREVENTION

This discussion would not be complete without consideration of the problem of prevention. The evidence seems conclusive that poor nutrition is an important factor in predisposing to the disease, although we fully admit and can confirm the occurrence of pellagra in persons well nourished and apparently robust. The investigation of the dietaries of the state institutions reveals no defect in quality or quantity. There does, however, seem to be a low animal protein content. The Italian peasantry have suffered more from pellagra than any other people, and their diet consists almost exclusively of maize in the form of polenta. They eat practically no meat, fish, milk or eggs. In fact, it may be said that meat becomes a luxury in all conditions of poverty. Maize has a large protein value, but this, apparently, cannot satisfactorily take the place of animal protein altogether. It may be then, that conditions in which the animal protein content of the diet is low, constitute a predisposing factor to infection with pellagra. In making this suggestion, we emphatically do not wish to be misunderstood. The dietaries of the state hospitals in Illinois are fully up to the usual standards in such institutions elsewhere and we do not consider that pellagra is due to lack of food or even to deficiency in any particular constituent of the food. Our impression is rather that pellagra is due to infection of the body with some micro-organism. It does seem possible, however, that a diet deficient in animal protein may so alter the body that the infecting organism has a better chance to grow.

CONCLUSIONS

In closing this report we feel that certain conclusions are advisable for the purpose of representing our views on the lines which should be followed in further studying and dealing with this problem. They are purposely expressed in somewhat general terms.

1. Pellagra is a disease due to infection with some living micro-organism.

2. A possible habitat for this parasite in man is the intestinal canal.

3. Deficient animal protein in the diet may constitute a predisposing factor in the contraction of the disease.

4. The number of cases of known pellagra renders this disease a decided menace to the public health of this state.

5. Careful search for, and investigation of, suspected cases outside the state hospitals for the insane is extremely desirable in view of experience elsewhere.

THE EFFECT OF THE TUBERCULO-TOXIN ON THE ADRENAL FUNCTION*

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The following work was undertaken for the purpose of producing an experimental chronic insufficiency of the adrenal glands. It was then our intention to study this experimental insufficiency in relation to the other glands of internal secretion, and to compare it with the clinical picture of Addison's disease.

Thus far all experimental work has resulted only in an acute insufficiency of the adrenal function. Excision of the glands is followed by death in two or three days. It was accordingly necessary to devise some means of slowly but progressively injuring the function of the glands. For this purpose it was decided to try the injection of tuberculin over long periods. Tuberculin was selected because of the evidence presented by certain workers in this field that chronic tuberculosis causes a sclerosis and atrophy of the adrenal glands.

Bernard and Bigard¹ have found, in the adrenals of the tuberculous, a sclerosis beginning at the vessels, causing lobulation of the glands, especially manifest in the cortex, but also invading the medulla. This can go on to complete atrophy in cases of intense sclerosis. Parisot and Lucien² have shown that the extracts of the adrenals of persons dying of chronic tuberculosis have a less intense hypertensive action than those of normal extracts. Boinet³ states that cases of adrenal sclerosis are more numerous than primary tuberculosis or cancer of the adrenals; and that this condition, with or without *melanodermie*, is common in the course of, or at the end of, pulmonary tuberculosis. The above mentioned workers believe that the anatomical and physiological changes noted by them resulted from the action of the tuberculo-toxin.

*From the Joseph Eichberg Laboratory of Physiology, University of Cincinnati.

1. Bernard, L., and Bigard: Les processus sécrétoires dans la substance corticale de la glande surrénale. *Compt. rend. Soc. de biol.*, 1905, lix, 504 (quoted by Boinet).

2. Parisot, J., and Lucien, M.: Etude physiologique et anatomique des capsules surrénales chez les tuberculeux. *Reunion biologique de Nancy*, 1907, lxiii, 525 (quoted by Boinet).

3. Boinet, E.: Opotherapie Surrénale dans la maladie d'Addison. *Bull. de l'Acad. de Méd., Paris*, 1909, series 3, lxii, 154.

It seemed reasonable to assume that Koch's old tuberculin⁴ contained these toxins; and that if the changes described by Bernard and Bigard, Parisot and Lucien, and Boinet, were caused by products resulting from the growth of the tubercle bacillus in the human body, we might expect to produce similar effects by injecting tuberculin into rabbits. It was thought better to use tuberculin⁵ rather than to inoculate the animals with living bacilli because in the former case we could regulate the dose and because we could be sure there were no tubercle bacilli in the adrenal glands.

Our experimental procedure was as follows: We employed two series of animals. In the first series we started with very small doses of tuberculin in order not to kill the rabbits should they develop the signs of a toxemia. The first injections were 0.01 gm. repeated daily. No evidence of disease being noted, we gradually increased the dose up to 0.10 gm. In the second series the dose throughout was 0.10 gm. In no case did the animals show any of the symptoms of a toxemia. They did not lose weight or strength, remained lively and ate well. In several instances they gained weight.

The two functions of the adrenal secretion which are most firmly established, are the glycogenic and the pressor. It has been shown by Porges⁶ and others that persons suffering from Addison's disease, and dogs from whom the adrenals have been excised, have an amount of glucose in the blood far below the normal. Subcutaneous injections of adrenalin, on the other hand, cause a transient hyperglycemia. A low blood-pressure occurs in the great majority, and perhaps in all cases of true Addison's disease. Injections of minute doses of adrenalin, on the other hand, cause a sharp rise in blood-pressure.

In order to find whether we had interfered with or destroyed the functions of the adrenal glands in our animals we in the first place compared the percentage of glucose present in the arterial blood of rabbits which

4. Koch's old tuberculin (H. K. Mulford & Co.) is prepared as follows: Tubercle bacilli are grown on glycerated broth for from thirty to sixty days. The culture is then poured into flat dishes and evaporated to one-tenth its original bulk over live steam. The filtrate from this concentrated broth is the finished product.

5. Concentrated old tuberculin was mixed with a sufficient amount of 0.9 per cent. salt solution to give the desired dilution. One c.c. of this solution was received into each of a series of ampoules; the latter were sealed and submerged in water; the water was boiled for five minutes. It was found necessary in the absence of a preserving fluid to take these precautions in order to maintain sterility.

6. Porges, O.: Zur Pathologie des Morbus Addison. *Ztschr. f. klin. Med., Berl.*, 1910, lxx, 243.

had received injections of tuberculin over a long period of time with that found in normal rabbits.⁷

A striking decrease in the glucose content of the blood was found. In Rabbit XXIII, after 4.55 gm. of tuberculin had been given in the course of four months; and in Rabbit XXXV, after 7.1 gm. had been given in the course of three months, the glucose was present in such minute amounts that no test with Fehling's solution could be obtained. It is interesting to note that, in these same rabbits, there was no definite hypoglycemia after Rabbit XXIII had received 0.81 tuberculin in the course of three months, and after Rabbit XXXV had received 3.1 tuberculin in the course of one month and a half. In another rabbit, No. XXV, after 4.31 gm. tuberculin had been given in the course of four months, an infinitesimal amount of glucose—0.006 per cent.—was found. This rabbit after receiving 0.87 gm. of tuberculin in the course of two months, showed a blood sugar content which equaled about 50 per cent. of the normal. Rabbit XXXIV, after 7.7 gm. of tuberculin in the course of three months showed less than half of its normal percentage of glucose. It would seem that the total length of treatment was a more important factor in determining the decrease in the blood sugar content than the total amount of tuberculin injected. The accompanying table shows clearly the effect of tuberculin on the per cent. of glucose in the blood.

In the next place we employed a method described by Cooke⁸ to find whether we had interfered with the pressor function of the adrenal glands in our experimental animals. Cooke wished to compare the pressor effect of the adrenals of a person dying of tuberculosis of the

7. The method used for determining the percentage of glucose in the blood was as follows: After fasting twenty-four hours, the rabbit was etherized, the carotid artery dissected free and bled into a 50 c.c. volumetric flask containing 5 c.c. of a 2 per cent. ammonium oxalate solution, until the flask was about three-fourths full. Distilled water was then run into the flask from a buret up to the 50 c.c. mark; the amount of water used, noted, and this plus 5 subtracted from 50 to determine the amount of blood obtained. To 200 c.c. of a 2-per cent. solution of HCl and 200 c.c. of a 5 per cent. solution of HgCl_2 , contained in a 500 c.c. graduate, the contents of the flask, and enough water to make 500 c.c. were added and the whole filtered. H_2S was passed through the filtrate until a black precipitate was obtained and this was then filtered and the amount of filtrate noted. From this the proportion of the original 500 c.c. remaining as filtrate, and so the proportion of the blood it contained, was calculated. The filtrate was neutralized with NaOH and evaporated to about 25 c.c. Fehling's solution was added in excess. The resulting precipitate was collected on an ash-free filter paper, washed until no reaction for sulphates was obtained, dried, ignited in a weighed porcelain crucible and weighed. This gives the weight of the CuO thrown down by the glucose. From this the amount of glucose in the original volume of blood, and so the percentage, is calculated.

8. Cooke, J. V.: Some Observations on the Blood-Pressure-Raising Substance of the Adrenals in Acute Adrenal Insufficiency. *THE ARCHIVES INT. MED.*, 1912, ix, 108.

adrenals, with that found in human beings dying of some other disease. He found that the diseased portions of the tuberculous adrenals caused no rise in the blood-pressure tracing of a dog, whereas, the extract of the "normal" adrenals caused a rise quite similar to that produced by injection of adrenalin. A "normal" rabbit was etherized, the carotid artery exposed and connected with a writing lever through a mercury manometer. The rabbit's normal pressure was written on a kymograph. One of the "treated" animals was killed, the adrenal glands removed, ground in a mortar with sand and ten volumes of salt solution added, and centrifugalized. A portion of the supernatant fluid was injected into the ear vein of the "normal" rabbit. It will be seen (Figures 1 and 2), that a sharp, marked rise occurred very quickly. We must conclude from these tracings that the pressor function of the adrenal secretion had either been interfered with very slightly or not at all.



Fig. 1.—Effect on blood-pressure of experimental injection of extract of adrenal gland in a rabbit: A. Intravenous injection of 2 c.cm. of the extract of the adrenal glands of Rabbit No. XXXV. B. Intravenous injection of 2 c.cm. of normal salt solution. C. Intravenous injection of 1 minim of adrenalin (P. D. & Co.). The marked pressor effect of the adrenal extract is apparent. This animal's blood contained so little glucose that no precipitate with Fehling's solution could be obtained.

If we now try to interpret our findings, we would say that the marked hypoglycemia produced would strongly suggest that an extreme degree of functional insufficiency of the adrenal secretion had been brought about. On the other hand, such a conclusion is not warranted, in the face of the fact that the pressor function remains intact and that none of the Addisonian symptoms were noted. Most of the data at our disposal lead us to believe that the glycogenic and pressor functions go hand in hand—that no marked alteration occurs in the one without affecting the other. In Addison's disease we find not only a hypoglycemia but also a low blood-pressure. After injection of adrenalin we get not only a hyperglycemia but also an increased blood-pressure.

The evidence which might be presented to show that changes can occur in the glycogenic function without involving the pressor function

TABLE SHOWING EFFECTS OF TUBERCULIN ON THE ADRENAL FUNCTION

Experiment No.	Per cent. Glucose in Blood Before Treatment.	Per Cent. of Glucose in the Blood after a Certain Number of Injections.	Per Cent. of Glucose in the Blood after Total Number of Injections.	Weight Before Treatment, Kilos.	Weight at End of Experiment, Kilos.	Remarks.
XXIII		Fifteen injections of tuberculin, 0.01 gm. each; \pm 9 injections of tuberculin, 0.2 gm. each; + 8 injections of tuberculin, 0.06 gm. each. 0.130.	Fifteen injections of tuberculin, 0.01 gm. each; + 9 injections of tuberculin, 0.02 gm. each; + 12 injections of tuberculin, 0.06 gm. each; + 35 injections tuberculin, 0.10 gm. each. 0.06.	1.9	1.9	The animal throughout the experiment was strong and active, and showed no evidence of disease.
XXIV	0.150	Nine injections of tuberculin, 0.01 gm. each; + 9 injections of tuberculin, 0.02 gm. each; + 10 injections of tuberculin, 0.06 gm. each. 0.082.	Nine injections of tuberculin, 0.01 gm. each; + 9 injections of tuberculin, 0.02 gm. each; + 14 injections of tuberculin, 0.06 gm. each; + 32 injections of tuberculin, 0.10 gm. each. 0.006.	2.0 1.9	2.2	Normal control. The animal throughout the experiment was strong and active, and showed no evidence of disease. <i>Thirty five days after the last injection of tuberculin the per cent. of glucose in the blood was found to be 0.097. It had returned to about the normal at age.</i>
XXV	0.098 0.133		Seventy-seven injections of tuberculin, 0.10 gm. each. 0.061.	2.0 2.7	2.7	Normal control. The animal throughout the experiment was strong and active and showed no evidence of disease.
XXVI		Glucose still present in marked amount after 31 injections of tuberculin, 0.10 gm. Precipitate of CuO lost.	Seventy-one injections of tuberculin, 0.10 gm. each. 0.0.	2.0	1.9	The animal throughout the experiment was strong and active and showed no evidence of disease. January 24, 1912, a litter of four born dead.
Averages	0.127		0.016.			

and *vice versa*, is not of a very convincing nature. Shur and Weisel,⁹ Goldzieher and Molnár,¹⁰ and Goldzieher¹¹ have tried to prove that the blood of chronic nephritics contains an excess of adrenalin; and they have attributed the high blood-pressure found in this disease to the action of this excess. If this were a fact we should have an example of a pressor effect without a corresponding glycogenic one. But O'Connor,¹² Bröking and Trendelenburg,¹³ and Falta and Flemming¹⁴ have shown that the methods used for determining the amount of adrenal secretion present in the blood serum, are faulty; and that, consequently, the conclusions based on these methods are not tenable. Falta¹⁵ has suggested that human diabetes mellitus might, in certain instances be the result of overfunction of the adrenal glands. If such were the case this would serve as an example of a glycogenic effect without a corresponding pressor effect. But we have no direct evidence in support of Falta's hypothesis.



Fig. 2.—Effect on blood-pressure of experimental injection of extract of adrenal gland in a rabbit: A. Intravenous injection of 0.8 c.c.m. of the extract of the adrenal glands of Rabbit No. XXXIV. B. Intravenous injection of 1.6 c.c.m. of normal salt solution. The marked pressor effect of the adrenal extract is apparent. This animal's blood showed a more than 50 per cent. reduction in the glucose content.

9. Schur, H., and Weisel, J.: Beiträge zur Physiologie und Pathologie des chromaffinen Gewebes. Wien klin. Wehnschr., 1907, xx, 1202.

10. Goldzieher, M., and Molnár, B.: Beiträge zur Frage der Adrenalinämie. Wien. klin. Wehnschr., 1908, xxi, 215.

11. Goldzieher, M.: Beiträge zur Pathologie der Nebennieren. Wien. klin. Wehnschr., 1910, xxiii, 869.

12. O'Connor, J. M.: Ueber Adrenalinbestimmung im Blute. München. med. Wehnschr., 1911, lviii, 1439.

13. Bröking, E., and Trendelenburg, P.: Adrenalin-nachweis, und Adrenalin-gehalt des menschlichen Blutes. Deutsch. Arch. f. klin. Med., 1911, ciii, 168.

14. Falta, W., and Flemming, G. B.: Ueber die Wirkung des Adrenalins und Pituitins auf den überlebenden Kaninchenuterus und über die Verwertbarkeit der Uterus-methode für den Adrenalin-nachweis im Serum. München. med. Wehnschr., 1911, lviii, 2649.

15. Falta, W.: Ueber die Gesetze der Zuckerausscheidung beim Diabetes mellitus. Ztschr. f. klin. Med., Berl., 1908, lxx, 300.

16. Fischer, Martin H.: Personal communication.

Martin H. Fischer¹⁶ has suggested that our findings might be explained on the basis of fever produced by the tuberculo-toxin which so increased the carbohydrate metabolism of the rabbit that there was produced within the organism a great reduction of the glycogen content. This explanation might be possible but it seems to us that such marked reduction in the amount of glycogen as would be required to produce such results as were obtained in Rabbits XXIII, XXV and XXXV must necessarily be accompanied by some of the symptoms of infection such as loss of appetite, loss of weight, languor and weakness; none of which occurred as may be seen by consulting the table. Rabbit XXXV lost 0.1 kilos but this is explained by the fact that it was weighed for the first time very near the end of pregnancy. Rabbits XXIII and XXXIV maintained a constant weight and Rabbit XXV gained 0.3 kilos. At no time during the course of our experiments did any of these rabbits show any sign or symptom of disease.

It is impossible in the present state of our knowledge to give a satisfactory explanation for the results we have obtained.

PROTOCOLS

Protocol 23.—Belgian hare. Male, 1.9 kilos. From June 11, 1911, to July 9, 1911, fifteen subcutaneous injections of tuberculin, 0.01 gm. at each injection.

From July 11, 1911, to July 27, 1911, nine injections of tuberculin, 0.02 gm. at each injection.

From July 28, 1911, to August 29, 1911, twelve injections of tuberculin, 0.06 gm. at each injection.

From August 30, 1911, to the end of the experiment November 5, 1911, thirty-five injections of tuberculin, 0.10 gm. at each injection.

August 13, 1911, blood from right carotid artery showed 0.130 per cent. glucose.

October 22, 1911, blood from left carotid artery showed *no precipitate with Fehling's solution*.

Protocol 24.—Black and white rabbit. Male, 2.6 kilos.

June 14, 1911, blood from right carotid artery showed 0.150 per cent. glucose. No further observation.

Protocol 25.—White rabbit. Male, 1.9 kilos.

From June 23, 1911, to July 9, 1911, nine injections of tuberculin, 0.01 gm. at each injection.

From July 11, 1911, to July 27, 1911, nine injections of tuberculin, 0.02 gm. at each injection.

From July 30, 1911, to August 29, 1911, fourteen injections of tuberculin, 0.06 gm. at each injection.

August 19, 1911, blood from right carotid artery shows 0.082 per cent. glucose.

From September 2, 1911, to November 5, 1911, thirty nine injections of tuberculin, 0.10 gm. at each injection.

October 29, 1911, blood from left carotid artery shows 0.006 per cent. glucose.

December 10, 1911, thirty five days after the last injections of tuberculin, blood from femoral artery shows 0.094 per cent. glucose.

Protocol 30.—White rabbit. Female, 2.0 kilos.

Blood from right carotid artery shows 0.098 per cent. glucose. No further observation.

Protocol 34.—White rabbit. Male, 2.7 kilos.

December 23, 1911, blood from right carotid artery shows 0.133 per cent. glucose.

December 28, 1911, to April 14, 1912, ninety injections of tuberculin, 0.10 gm. at each injection.

April 1, 1912, blood from left carotid artery shows 0.061 per cent. glucose.

April 15, 1912, animal killed by a blow on the head. Adrenal glands removed and macerated in salt solution; 2 c.c. injected into the ear vein of a normal rabbit writing blood-pressure as shown in Fig. 2.

Protocol 35.—Black and white rabbit. Female, 2.0 kilos. January 8, 1912, to April 6, 1912, seventy-five injections of tuberculin, 0.10 gm. at each injection.

January 24, 1912, a litter of four born dead.

February 16, 1912, blood from right carotid artery shows a definite glycemia. Precipitate lost.

April 2, 1912, blood from left carotid artery shows *no precipitate with Fehling's solution*.

April 7, 1912, animal killed by a blow on the head. Adrenal glands removed and macerated in salt solution. Two c.c. injected into the ear vein of a normal rabbit writing blood-pressure as shown in Fig. 1.

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STUDIES IN AUSCULTATORY BLOOD-PRESSURE PHENOMENA *

I. THE EXPERIMENTAL DETERMINATION OF DIASTOLIC PRESSURE

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INTRODUCTION

The increasing conception of the importance of blood-pressure determinations as aids in medical diagnosis has led to considerable work on this subject.

Since Korotkoff,¹ in 1905, demonstrated his auscultatory phenomenon there has been a gradual adoption of this method following the recommendations of workers who have made comparative readings with this and Uskov's sphygmomanometer, von Recklinghausen's tonometer and Pal's sphygmoscope. As there seemed still to be a difference of opinion regarding the point where the diastolic pressure should be read, the majority of German authors holding that it should be read at the so-called fourth phase where the loud sound suddenly becomes dull, the Americans using the disappearance of all sound, the fifth phase, as diastolic pressure reading, an attempt was made to settle the question by actually recording pressure and sounds simultaneously on dogs.

THE DIASTOLIC PRESSURE AND ITS DETERMINATION

Howell and Brush² were the first to show experimentally that the maximum oscillations of a lever attached to a mercury column corresponded to the diastolic pressure. This was further delimited by Erlanger and Hooker,³ who, working with normal men with the former's instrument, showed that the point where diastolic pressure should be read was at the sudden diminution of the size of the maximum oscillations. In an elaborate critical review of the literature bearing on blood-pressure, and particularly diastolic and pulse-pressure, with the relation of the pulse-pressure to the velocity of blood-flow, they concluded that there was some relationship between the velocity of blood and the pulse-pressure which

*From the Physiologic Laboratory of the University of Wisconsin, Prof. J. A. E. Exster, Director.

1. Korotkoff: Zur Methodik der Blutdruckmessung, Mitt. d. k. mil. med. Akad. zu St. Petersburg, 1905, xi, 365.

2. Howell and Brush: A Critical Note upon Clinical Methods of Measuring Blood-Pressure, Boston Med. and Surg. Jour., 1901, cxlv, 146.

3. Erlanger and Hooker: An Experimental Study of Blood Pressure and of Pulse Pressure in Man, Johns Hopkins Hosp. Rep., 1904, xii, 115.

could be expressed as $\text{velocity} = \text{pulse-rate} \times \text{pulse-pressure}$. They, however, were careful to call attention to several modifying factors, but on the whole they thought that given certain constant factors all of which would hardly change at one time, the relationship between pulse-pressure and velocity held good. Dawson and Gorham,⁴ in an experimental study of the relationship of pulse-pressure to systolic output, conclude that "under normal conditions and during various procedures (namely, stimulation of the vagus centrally and peripherally, saphenus nerve centrally, and of the annulus vieussentis, intravenous transfusion of 0.5 per cent. sodium chlorid solution, intra-arterial transfusion of strong carbonate, bleeding and asphyxia) the pulse-pressure is a reliable index of the systolic output."

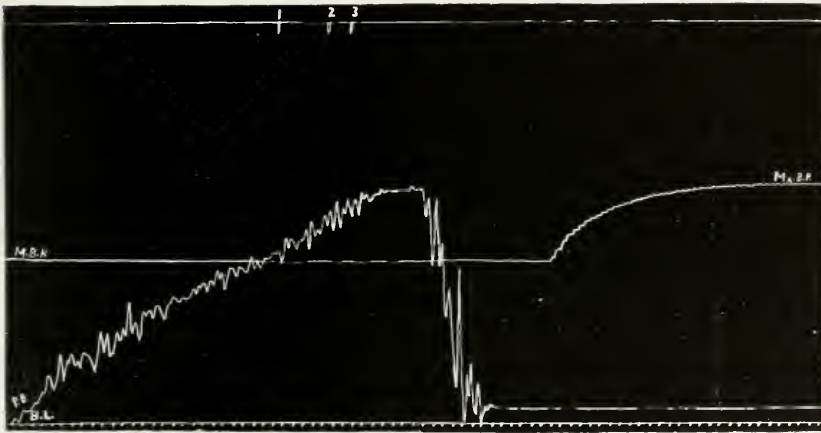


Fig. 1.—All figures are to be read from left to right. The top line records the points where sounds were heard, the figures above the short vertical lines refer to tones (see text). Mx. B. P., maximum blood-pressure. M. B. P., minimum blood-pressure. P. B., pressure bulb recorder. It was impossible to lower and raise this bulb by hand without obtaining the great irregular oscillations of the attached lever above the mercury manometer. B. L., base line.

There have been described four methods of estimating the diastolic pressure: 1. The oscillatory (Janeway, Masing). 2. The palpatory (Strasburger, Hirschfelder). 3. The graphic (v. Recklinghausen, Erlanger). 4. The auscultatory (Korotkoff).

Korotkoff in his original communication called attention to the fact that the diastolic occurred at the end tone, that is, at the point where the clear third tone was suddenly replaced by a dull tone. His reasons were theoretical.

4. Dawson and Gorham: The Pulse-Pressure as an Index of Systolic Output, *Jour. Exper. Med.*, 1908, x, 484.

Fischer⁵ found the oscillatory maximum and minimum and compared them with the auscultatory maximum and minimum. He used the v. Recklinghausen instrument. He found that in 150 cases the oscillatory and auscultatory minimum were equal in forty-seven cases. In fifty-five the oscillatory was practically equal to the auscultatory, 1 to 3 mm. Hg less, negligible values. In twenty-four the difference was 4 to 6 mm.; in twelve cases 12 to 16 mm. In 102 cases with the v. Recklinghausen instrument, therefore, there was agreement between oscillatory and auscultatory minimum. Fischer arrived at the conclusions that the auscultatory method of measuring blood-pressure was the most accurate and that the diastolic reading occurred at the so-called fourth phase, i. e., when the loud tone of the third phase suddenly becomes dulled.

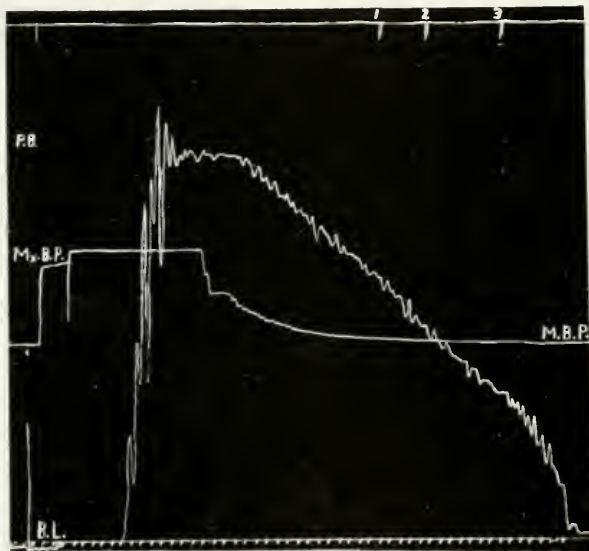


Fig. 2.—Tracing of auscultatory phenomena. See explanation in legend of Figure 1.

Lang and Manswetona⁶ compared the auscultatory method of Korotkoff with the graphic method on the v. Recklinghausen tonometer. They found that the onset of the third tone was coincident with the greatest oscillation of the tonometer. They stated that the auscultatory method could not be applied to dogs. It is not clear in their description just what method they used in their work on dogs. They speak of a physiological

5. Fischer, J.: Die Auskultatorische Blutdruckmessung im Vergleich mit der oscillatorischen von Heinrich von Recklinghausen und ihr durch die Phasenbestimmung bedingte Wert, *Ztschr. f. diätet. u. physik. Therap.*, 1909, xii, 389.

6. Lang and Manswetona: Zur Methodik der Blutdruckmessung nach v. Recklinghausen und Korotkoff, *Deutsch. Arch. f. klin. Med.*, 1908, xciv, 141.

and clinical method and say that they had success in dogs only with the oscillatory method. From their experiments they concluded that the diastolic pressure was coincident with the change from the greatest oscillation to one definitely smaller.

The diastolic pressure is not, according to them, to be taken when the oscillations are largest, but at the place where the greatest oscillations become suddenly smaller or where the ordinary loud tone gives place to a dull tone, viz., at the so-called fourth phase (Ettinger⁷).

At the moment when one notes the first decrease in size of the greatest oscillations, the Korotkoff tone becomes suddenly weaker, then soon ceases, or suddenly the tone vanishes entirely. This first decrease in size of the largest oscillations and the first dulling of Korotkoff's end-tone marks the diastolic pressure and not the end of the large oscillations and the complete disappearance of all sound phases.

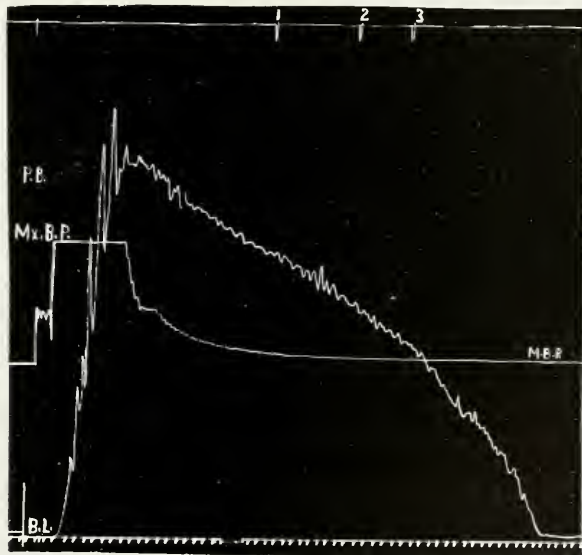


Fig. 3.—Tracing of auscultatory phenomena. See explanation in legend of Figure 1.

Erlanger⁸ demonstrated with his instrument that by the method of continuous escapement the diastolic pressure was at a point where the maximum oscillations suddenly became smaller. His readings were within 5 mm. of the actual diastolic pressure. By means of the intermittent escapement he obtained records showing this same point. He made an artificial circulation schema using among other materials a piece of

7. Ettinger: Die auscultatorische Blutdruckmessung nach Korotkoff. Wien. klin. Wchnschr., 1907, xx, 992.

8. Erlanger, J.: A New Instrument for Determining the Minimum and Maximum Blood-Pressures in Man. Johns Hopkins Hosp. Rep., 1904, xii, 53.

recently removed artery which was placed in a plethysmograph and connected with a manometer and with a pressure bottle. He proved that the diastolic pressure was coincident with the greatest expansion of the artery and he noticed that when the artery was expanding to its fullest extent at every pulsation there was a clicking tone produced. Van Westenrijk⁹ made comparative readings with the auscultatory method and the Uskov sphygmomanometer and with Pal's sphygmoscope. He considered that his experiments showed that the greatest excursions of the lever of Uskov's instrument and the greatest oscillations of Pal's instrument were coincident with the second clear tone heard with the stethoscope (the third phase). He found that the sudden fall in maximum excursions was very near or at the disappearance of all tone in the majority of cases studied.

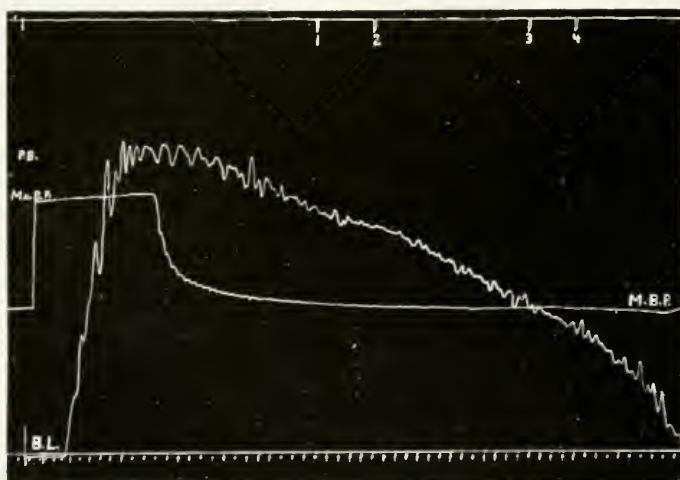


Fig. 4.—Tracing of auscultatory phenomena. See explanation in legend of Figure 1.

Hirschfelder¹⁰ mentions some determinations made at the Johns Hopkins Hospital with the Erlanger instrument and the auscultatory method which seemed to show that the disappearance of all sound, the fifth phase, was the point where diastolic pressure should be read.

Articles in American literature (Gittings,¹¹ Goodman and Howell¹²) have considered the disappearance of all sound as the diastolic pressure.

9. Van Westenrijk, N.: Ueber die Beziehungen der Tonmethode der Bestimmung des Maximal- und Minimal-Blutdrucks zu den übrigen Methoden und über die Bedeutung dieser Grössen, *Ztschr. f. klin. Med.*, 1908, lxxvi, 465.

10. Hirschfelder, A. D.: *Diseases of the Heart*, etc.

11. Gittings, J. C.: The Auscultatory Blood Pressure Phenomenon, *THE ARCHIVES INT. MED.*, 1910, vi, 196.

12. Goodman and Howell: The Auscultatory Blood-Pressure Phenomenon, *Univ. Penna. Med. Bull.*, 1910, xxiii, 469.

and have seemingly ignored the most important of the German articles, taking Ettinger's word that the disappearance of all sound was the point where the diastolic pressure should be measured.

EXPERIMENTAL DATA

The problem was: Is it possible to use the auscultatory method to prove experimentally that a certain change of tone and not the disappearance of all sound, indicates the point to read diastolic pressure?

Method and Apparatus.—Dogs were etherized and a tracheal cannula placed in the trachea connected with the usual ether bottle. It was aimed to produce uniform narcosis throughout a series of observations on a dog. The right femoral artery was connected with a mercury manometer the

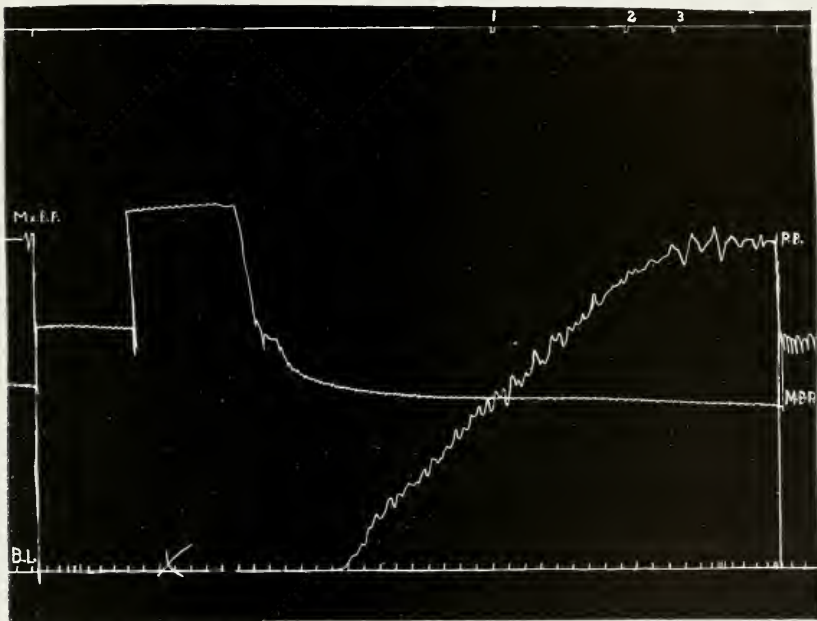


Fig. 5.—Tracing of auscultatory phenomena. See explanation in legend of Figure 1.

lever of which wrote on a revolving drum. In this pressure system a Dawson maximum and minimum pressure valve was introduced so that the pressure could be held either at systolic or at diastolic pressure. The left femoral artery was exposed freely, Poupart's ligament was cut so as to give as little chance as possible for undue compression; at first the artificial pressure chamber devised by Erlanger⁸ was tried, but it failed to work. Two small cups $\frac{1}{2}$ inch deep were made. From two opposite poles of each cup tubing led off. The rim of each cup on two opposite poles was cut out a trifle. Rubber dam was then tied over each cup rather

loosely and this was connected with a vessel of water which could be raised or lowered, and to a mercury manometer which recorded the pressure in mm. of Hg. The writing lever was arranged to mark at, or very near, the blood-pressure marker. A timer on the base line and a lever attached to a key which, when pressed, made a mark on the drum record, completed the apparatus. An assistant held in place the cups one above, one below the artery, another manipulated the drum and the pressure bottle and I listened over the femoral artery, distal to the point of compression, using a stethoscope with a small bell. Records were made with descending and ascending pressure.

A typical record was made as follows: The compression chamber was securely held around the femoral artery and the stethoscope placed from

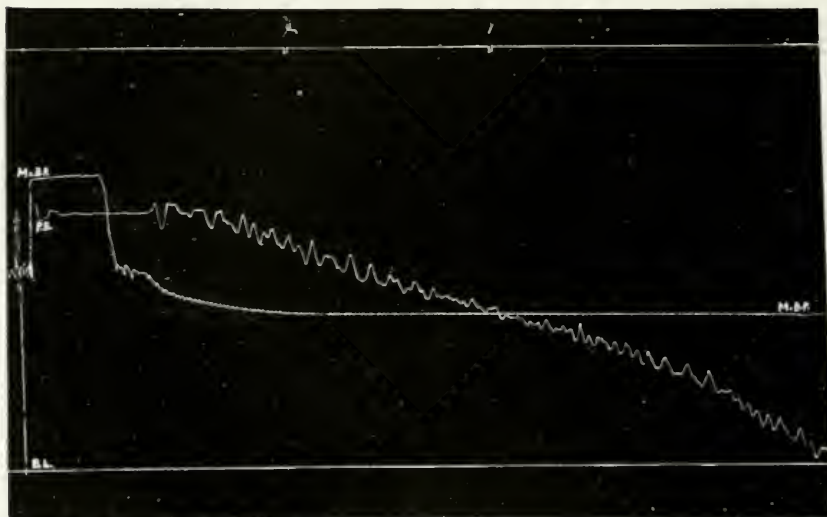


Fig. 6.—Tracing of auscultatory phenomena. See explanation in legend of Figure 4.

2 to 3 cm. below on the skin or muscle directly over the artery. The pressure in the bulb was now raised above systolic pressure, the drum started, the maximum and minimum valve turned to minimum and the bulb gradually lowered. It was impossible to lower this vessel gradually without giving irregular waves on the kymograph. Without being able to see (my back was to the drum) I pressed the marker key (the line at top of all records) when there was change of sound and called the diastolic when I heard the tone change at the time the key was pressed. The object was to find if a certain definite change of tone was coincident with the diastolic pressure. When the line made by the lever of the pressure-bulb connection crossed that of the diastolic pressure it was thought that a

change of tone might occur which could be recognized as corresponding to the diastolic pressure. The study of the records from the three dogs shows that this was possible both with ascending and descending pressure.

The sounds in an artery of a dog as pressure is released and more and more blood flows through the compression site are not like those of man. There are several reasons for this. In the first place, the artery (except in very large dogs) is smaller than the brachial artery of man. It is known that the Korotkoff tones cannot, for example, be heard over the radial artery. The artery must not only be of some size, but it must be so situated that the stethoscope bell can be actually placed over it on the

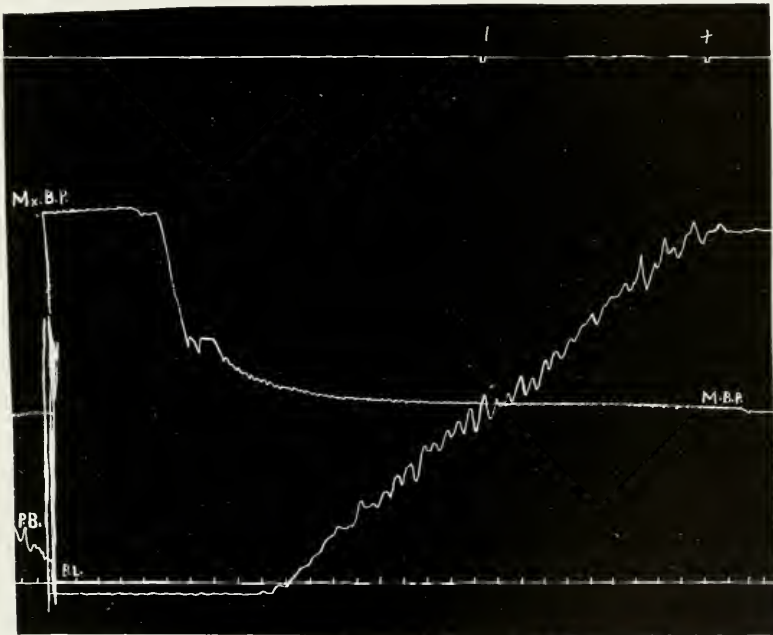


Fig. 7.—Tracing of auscultatory phenomena. See explanation in legend of Figure 1.

skin without compressing the vessel. In the second place, the femoral artery is almost directly in a line with the aorta, and there is only one large branch (the internal iliac) which receives a comparatively small amount of blood. The velocity in the femoral, especially when there is vasodilatation, is almost equal to that in the aorta. The tones depend on velocity of blood flow through the artery for their production (Fischer,⁵ Ettinger,⁷ etc.). Therefore, in an anesthetized dog with marked vasodilatation there may be a sound even when no compression is made on the artery, comparable to the sound heard in aortic insufficiency in man when the pulse-pressure is practically equal to the systolic pressure. In the

third place, there is a marked vasodilatation in the circulation of an etherized dog, the peripheral resistance becomes less, the systolic pressure is at the same time raised so that at each systole of the heart the blood rushes into a partially collapsed vessel and distends it to its utmost. Erlanger* has already shown that such a condition produces a shock and a sound.

Every one of the three dogs showed differences of tone on releasing the compression around the artery. It was necessary to spend some time learning the quality of the tones in order to determine, (1) the characters of the tones heard, (2) the sequence of the cycle of tones. From twelve to eighteen observations were made on each dog.

Dog 1.—May 17, 1912. Fox terrier dog, weight 10 kilos. With pressure rising from 0 (Fig. 1), the first tone heard in this dog's femoral artery was a dull tone which exactly corresponded to diastolic pressure; that is, where the pressure on the artery equaled the minimum pressure in the other femoral artery. This dull tone soon gave place to a sharp clear tone at mark 2. There was then a series of murmurs to be heard ending in a tone at mark 3, somewhat similar to the first tone heard.

It will be noted that practically all tones are present in this particular artery although it was extremely difficult to differentiate them on account of the comparatively faint sounds. Only the lower and upper 1 and 3 were easily made out. On the records the position of 2 was variable. The first dull tone occurred at diastolic pressure in this series, the last dull tone occurred at or near systolic pressure. In the second series from the same animal two figures are shown. It was found difficult always to catch the first sound at systolic pressure by the decrease of pressure corresponding to continuous escapement. Thus in Figure 2 it is seen that the first mark heard is at a point below the maximum pressure, whereas the second mark records the change of tone corresponding to the change in man from the third to the fourth phase, and the third mark is at the disappearance of all sounds. This record shows clearly that the change of tone occurs practically at diastolic pressure and the disappearance of sound is well below the diastolic pressure.

In Figure 3 of this series a slightly different record is seen where the first sound, which was carefully listened for, occurred at maximum pressure and again the change from sharp to dull occurred just at diastolic pressure. The stethoscope was removed before all sound had ceased. There is thus no mark for the disappearance of sound.

This animal was the most satisfactory of the three, as there was the sharpest differentiation of the sounds although the sounds were faint and absolute quiet was necessary in order to hear them, and a number of records taken all showed the same correspondence between the change of the sharp tone to the dull tone at diastolic pressure.

DOG 2.—May 17, 1912. Bitch, weighing 11 kilos. Figure 4 is a typical record among a number taken from this animal. The first sound heard is indicated at the mark 1 and corresponds to maximum pressure. The second mark was at or near the point of maximum intensity of the clear sound. This suddenly became dull at mark 3 which is at diastolic pressure and at mark 4 there was a disappearance of all sound below maximum pressure. No records were taken from this dog with ascending pressure.

DOG 3.—June 5, 1912. Collie weighing 20 kilos. This animal did not prove very satisfactory. There was an exceedingly high blood-pressure, evidently due to the ether. The heart though normal beat powerfully and the pulse-pressure was 130 mm. Hg. as much as the usual maximum pressure. It was impossible to get a disappearance of all sounds. However, in the first series (Fig. 5), as an example, the first change of tone as the pressure was raised from 0 is seen to be directly at diastolic pressure. As it was not possible to raise the pressure bulb up high enough to compress the artery completely, the systolic sound could not be obtained from any of the records.

In series two, of which Figure 6 is an example, it is seen that the artery was not completely compressed. At X was a loud sound probably corresponding to the third in man: before that there was a sound murmur phase. At 1 there was a noticeable sudden dulling of the tone which gradually faded off into the tone heard over even the uncompressed artery. It is seen that this mark 1 is just at diastolic pressure.

It has not been possible to carry further a larger series, nor does it seem of any advantage, since the three animals showed, with minor variations in individual tones, the same essential features.

SUMMARY

There are auscultatory tone phases in the femoral arteries of dogs which correspond in a general way to those in man. The systolic pressure is at the point where the first tone is heard as the blood rushes under the site of compression. The diastolic pressure is not at the point of disappearance of sound when the pressure is gradually reduced, or at a point corresponding to that (as in Dog 3), but occurs when the first dull tone is heard following a loud, sharp tone.

It is possible in dogs to measure accurately the diastolic pressure by the auscultatory phenomena, using as the point of diastolic measurement the sudden change of tone from the maximum sound heard to a dull sound. It is therefore concluded that the point where diastolic pressure should be read is at the tone change from clear to dull, not at the point where all sound disappears. This is, as a rule, an appreciable interval below diastolic pressure. In man this point where diastolic pressure should be read is just at the point where the third clear tone phase suddenly becomes a dull sound.

The author wishes to express his thanks to Prof. Eyster and to Dr. Meek without whose active interest and cooperation the research would have been impossible.

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THE PERSISTENCE OF ACTION OF THE DIGITALINS *

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An attempt has been made in the present research to determine approximately the length of time during which the action of several of the digitalins persists after the introduction of suitable doses directly into the circulation, with the hope of throwing some light on their so-called cumulative action.

One finds many references in the literature to this so-called cumulative action of the digitalins, but there have been few investigations of the phenomena other than clinical.

The term cumulation is used somewhat loosely, but it is generally understood to mean the action which is manifested rather suddenly after the continued use of doses which singly do not cause perceptible effects.

Van der Heide¹ states that Mègevaud was the first to study this subject by means of animal experimentation in 1879, but the research was incomplete, so far as cumulation was concerned, since that investigator was interested mainly in the histologic changes induced in certain organs during chronic digitalis poisoning.

Schmiedeberg² states that the three digitalis principles, digitalin, digitalin and digitoxin, are absorbed with relative difficulty and slowly excreted, and on these factors the so-called cumulative action of digitalis is dependent in part; in part on a storage of the active substance in the organism when digitalis is used for prolonged periods during renal disturbance.

These deductions of Schmiedeberg's appear to be based on theoretical considerations; at least, I am not aware of any experiments on which they are based directly, and certain of the digitalins appear to be excreted through the gastro-intestinal tract to a greater extent than through the kidneys.³

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¹ From the Laboratory of Pharmacology, Cornell University Medical College, New York.

² The expenses of this investigation were borne in part by the Therapeutic Research Fund of the American Medical Association.

1. Van der Heide: *Arch. f. exper. Path. u. Pharm.*, 1885, xiv, 127.

2. Schmiedeberg: *Arch. f. exper. Path. u. Pharm.*, 1883, xvi, 185.

3. Hatcher: *Am. Jour. Physiol.*, 1909, xviii, 303.

Van der Heide¹ investigated the cumulative action of helleborein after injecting it subcutaneously into rabbits, and that of digitalin and helleborein administered to dogs by the mouth and rectum, and subcutaneously.

Owing to his employment of these several modes of administration, and of varying amounts of the drugs at irregular intervals, and even of both drugs in the same experiment, in some instances, it is difficult to form a correct opinion of the value of the conclusions at which van der Heide arrived. His results are complicated still further by the fact that he used an impure digitalin, which consisted of digitalein mainly, and this was dissolved in a 3 per cent. infusion of digitalis for subcutaneous injection; hence his results are due to the use of digitalis rather than to true digitalin, in those experiments where helleborein was not employed.

Van der Heide calls attention to the fact that the word cumulation indicates that the phenomena were attributed to a storage of the active principles in the organism, but he remarks that the earlier writers had no very clear conception of the method by which storage took place, and I might add that the same degree of uncertainty still exists.

He concluded that the dog and rabbit showed cumulative symptoms so far as the cardiac effects were concerned, and habituation on the part of the nervous system.

The next important pharmacological investigation of this cumulative action of the digitalins was made by Fraenkel,⁴ who administered several of the digitalins to cats by subcutaneous injection and attempted to observe the cumulation by means of the slowing of the pulse-rate, by the onset of gastro-intestinal symptoms, and by the death of the animal, following the repeated injection of doses which were individually too small to produce these effects.

Fraenkel's conclusions have been quoted very frequently, but I believe that he made important errors, and, since certain of his statements are irreconcilable with mine, it will be necessary to discuss some of his experiments later in connection with my own.

Cloetta⁵ tried to estimate the storage of one of the digitalins in the hearts of frogs and rats which had been poisoned with large amounts of the drug, but he was unable to detect even traces of the poison in that organ.

Schliomensun⁶ found that a group of substances (alcoholic phosphatids) could be isolated from the hearts taken from the human cadaver and from the dog, and that these substances appeared to possess an especial capacity for combining with the digitalins chemically, while the

4. Fraenkel: *Arch. f. exper. Path. u. Pharm.*, 1903, li, 84.

5. Cloetta and Fischer: *Arch. f. exper. Path. u. Pharm.*, 1906, liv, 294.

6. Schliomensun: *Arch. f. exper. Path. u. Pharm.*, 1910, lxiii, 294.

corresponding fractions obtained from the livers and skeletal muscles had no such affinity.

This observation of Schliomensun's would seem to indicate the possibility of storage of the digitalins in the heart.

Straub⁷ concluded that no storage of ouabain occurred in the tissues of the heart, as a result of his perfusion experiments, in which he found that the poison could be washed from the heart before it stopped beating by merely substituting fresh Ringer's solution for the poisoned perfusion fluid.

Lhoták von Lhota⁸ studied chronic digitalis poisoning induced in rabbits by oral and subcutaneous administration, and concluded that rabbits showed cumulative effects up to the tenth day of the poisoning, and tolerance thereafter.

The use of the rabbit for this type of experiment, and the employment of the digitalins by oral and subcutaneous administration for these investigations will be discussed in connection with my own results with such experiments.

CAUSES OF ACCUMULATION, SO-CALLED

Absorption and excretion play an important rôle in the so-called cumulative actions of the digitalins, but it is an extraordinary fact that we know almost nothing about either of these processes, except that the rate of absorption of these bodies from the alimentary tract is variable.

One finds extremely loose statements in the literature concerning the length of time during which the digitalins remain in the blood-stream after their introduction into the circulation, but so far as I have been able to learn these statements are not supported by experimental evidence, and the crude attempts made by van der Heide to detect the digitalins in the organs and the circulating blood are hardly worthy of mention; but the matter assumes much importance in view of the statement made by Straub,⁷ that the standstill of the perfused frog's ventricle depends on the concentration of the poison in the perfusing fluid and not on the total amount which passes through the heart, and that during perfusion no storage (in the common acceptance of the word) takes place in the tissues of the frog's heart.

It may be stated here that experiments still in progress in our laboratory show that practically all of a fatal dose of ouabain leaves the blood-stream within about three minutes after its injection into the veins of a cat, and we have also found that the cat's heart is poisoned promptly when ouabain is injected in extremely dilute solutions (1-250,000) at such a rate that its dilution in the blood-stream must be less than one in five hundred millions if it leaves the circulation as rapidly under these

7. Straub: *Biochem. Ztschr.*, 1911, xxx, 392.

8. von Lhota, L.: *Arch. int. de pharm. et de therap.*, 1910, xx, 451.

conditions as it does when it is injected more rapidly, and if such is the case there can be little doubt that the action of ouabain on the intact mammalian heart depends on the total amount which passes through the heart, and not on the concentration in which it exists in the blood, for the concentration just mentioned is vastly less than that which Straub found necessary to bring the perfused frog's heart to a standstill.

The slowing of the pulse-rate and the cardiac irregularity, which may be induced in many animals by the continued use of suitable doses of the digitalins have been utilized by several observers for the study of the onset and duration of the digitalis action, but it is true, nevertheless, that the effects of digitalis on the heart-rate in the cat are quite variable and many of my myographic tracings, taken at various intervals of time following the intravenous administration of large doses of the digitalins, give no visible evidence of their action on the heart, and in many cases these tracings are in no way different from those taken from normal animals; but it is impossible to suppose that the digitalins so administered have produced no *action* whatever, though the *effects* of such action are not perceptible in the tracings.

Even in those animals in which digitalis causes slowing of the pulse rate, that effect is induced only after the administration of fairly large doses. If, for the sake of illustration, we accept 25 per cent. of the fatal dose as the minimum amount which will be required in a given case to slow the heart-rate appreciably, it follows that this effect will persist only until elimination has reduced the amount in operation to a point where it becomes ineffective, at which time even a small dose will suffice to raise the amount in operation to the effective point and slowing will be induced again; for the smallest dose which produces measurable symptoms must consist of fractions which singly are insufficient to produce measurable effects.

This latent digitalis action often escapes attention in man and it may then become the basis for the so-called cumulative action, because of the small additional amount of the drug which then suffices to raise the action to the level where toxic symptoms are manifested.

This is understood readily when one remembers that the full therapeutic effect of digitalis is separated from the toxic action only by an imaginary line.

Briefly, then, one may investigate the so-called cumulative action of the digitalins by studying their absorption and excretion; by determining the length of time during which these principles remain in the bloodstream after they have entered the circulation; he may study the question of their storage in the tissues, particularly in the heart and nervous system; he may attempt to determine the duration of action by observing the objective symptoms, such as the slowing of the pulse-rate and the

cardiac irregularity, which they induce, as Fraenkel did; or, he may estimate directly the degree to which the previously administered drug is still effective, and the length of time during which the action persists.

As a matter of fact, while casting about for the best means of investigating the subject I have experimented along nearly all the lines just mentioned, but the methods which I have employed are quite different from those used previously, and the results of these investigations will be published in a series of papers.

In the research with which this paper deals I have attempted to estimate the latent action of the digitalins as well as that which induces symptoms which are readily observed; in other words, I have tried to determine the length of time during which the action of a single large dose, or repeated doses, of these bodies persists, and the relative intensity of the persisting action after a given interval of time.

TECHNIC

The following method was used in estimating the persistence of action of the digitalins in the cat and dog in the larger number of experiments which I have to report:

The fatal dose of the digitalis body for a given species was determined in a series of experiments in which the drug was injected slowly and continuously from a buret into the veins of the animals until death resulted after the typical symptoms of digitalis poisoning.

Having thus determined the fatal dose of a digitalin, a toxic, but not fatal, dose of the drug in measured amount was injected from a hypodermic syringe into the veins of a normal animal, which was then kept under observation for the required period of time, varying from one to thirty days. The animal was then placed on the operating board and the amount of the drug which was then required to cause death was determined in the way just described for a normal animal.

The difference between the fatal dose for the test animal which had previously received the initial dose and that required by a normal animal of the same weight must be due to the persisting action of the initial dose.

The following, taken from the protocol of an experiment, will serve to illustrate this method of estimating the persistence of action of digitalis:

May 16, 1912: Cat, female, weight 2.55 kg.; 11:31 a. m., heart-rate 248 per minute; 11:31½, heart-rate 207 per minute; 2:45 p. m., heart-rate 210; cat much excited; 2:55, injected 80 mg. digitalis per kg. by vein; 4:05, emesis.

May 17: 10:32 a. m., animal depressed; heart-rate 258-252.

May 18: 10:05 a. m., appears nearly normal; heart-rate 210.

May 20: 1:25 p. m., appears quite normal; heart-rate 256.

May 24: 10:00 a. m., anesthetized; digitalis injected slowly by vein; 10:48, toxic symptoms; injection stopped; 10:52, animal died; 62 mg. digitalis per kg. of body-weight had been injected.

A normal cat requires a dose of 100 mg. of digitalis per kg. of body-weight to cause death, but the test animal in the experiment just cited required only 62 mg. per kg. — a difference of 38 mg. per kg. — which represents the persistence of action of the initial dose after an interval of eight days.

I have used ouabain (the so-called crystalline strophanthin of Thoms) for estimating this latent action of the digitalis principles in nearly all of the experiments recorded in Tables 1 to 5, inclusive, and Table 7 and 10, because of the greater accuracy which is permitted by its use. When ouabain was not used the fact is so stated in the footnotes accompanying the tables.

The use of ouabain in this way is based on the results obtained by Hatcher and Brody,⁹ who found that ouabain and the various digitalins were capable of replacing each other in the estimation of the fatal dose; for example, if 50 per cent. of the fatal dose of digitoxin and 50 per cent. of the fatal dose of ouabain were injected into the veins of a cat the effect was the same as that which followed the injection of a fatal dose of either ouabain or digitoxin alone, except for the fact that when ouabain was used with digitoxin in this way death resulted more promptly than when digitoxin was used alone, because of the comparative slowness with which just fatal doses of digitoxin act, whereas ouabain acts promptly when just fatal doses are administered, and, curiously, the combination of fractional doses of digitalis or digitoxin with ouabain also acts promptly.

This permits of greater accuracy in the estimation of the fatal dose of digitalis or digitoxin than would be possible were either of those bodies used alone in the manner previously described.

The employment of ouabain also permits of a more accurate determination of the latent action of digitoxin, digitalis and other digitalins, than would be possible by means of those digitalins themselves for the final test: and furthermore, the insolubility of certain of these principles, such as digitoxin and digitalin, interferes with their slow and continuous intravenous administration.

The following protocol (in brief) of an experiment illustrates this method of estimating the latent action of a digitalin:

April 16, 1912: Cat, gray striped, female, weight 2.2 kg. 3:35 p. m., 0.4 mg. digitoxin per kg. in 3.2 c.c. 6 per cent. alcohol, by vein; 4:15, emesis; 4:25, convulsion; 4:50, symptoms suggest that dose is fatal.

April 17: 3:15 p. m., attempts to vomit; death seems imminent.

April 20: 9:30 a. m., weight 1.9 kg.; heart is very rapid; 11:22 ouabain in 1-100,000 solution, by vein; 11:49, death after 0.026 mg. ouabain per kg., or 26 per cent. of the average fatal dose.

Since the animal received 26 per cent. of the average fatal dose of ouabain four days after the initial dose of digitoxin, it follows that 74 per cent. of the fatal dose was attributable to the persistence of action of the digitoxin.

When the interval between the first dose and the final test is only a few hours or a day the sum of the amounts injected is almost the same

9. Hatcher and Brody: *Am. Jour. Pharm.*, 1910, lxxxii, 360.

as that which would be required at a single injection to cause death, because the effects of a fairly large dose of digitalis or digitoxin persist almost unchanged for a day.

When the interval following the administration of a given initial dose is as much as a week, the amount required to cause death at the time of the final test is somewhat variable because elimination takes place at very different rates in different animals; but even as late as a month after the intravenous injection of a nearly fatal dose of digitalis the test animal may require less than a normal animal would to cause death, showing that the action of digitalis sometimes persists even after such a long interval during which there has been no drug administered.

NATURE OF PERSISTING ACTION

It will suggest itself at once that this difference between the amount required to kill the normal, and that required to kill the test, animal after such a long interval of time is to be attributed to injury which the heart has sustained from the initial action of the digitalis rather than to any digitalis still operating on the heart.

Against such an argument is the fact that the cat's heart may be poisoned to an equal degree with ouabain, and after an interval of twenty-four to forty-eight hours following a nearly fatal dose the animal behaves like a nearly normal one, requiring almost as large a dose to cause death as a normal animal of the same weight would require.

The rabbit may be given a very nearly fatal dose of digitalis or digitoxin (the action of which is extremely persistent in the cat), but after two or three hours, the heart has so far recovered its normal condition that it will require a full fatal dose to cause death.

One might suppose this rapid elimination of digitoxin and digitalis by the rabbit to be due to habituation, but it follows the first dose.

It is difficult to account for the great differences in the persistence of action of the several digitalins in the same animal, or in that of the same digitalin in different animals, except on the hypothesis that the digitalins are eliminated at very different rates.

I have determined the fatal dose and the persistence of action of a number of the digitalins for the cat in the manner described, and have attempted to carry out similar experiments on other animals, including the dog, rabbit and guinea-pig, with some of the more important members of the digitalis group, but this was not feasible and a different procedure had to be adopted with the rabbit, while the attempt to use the guinea-pig for the experiments was abandoned.

The white rat shows nervous symptoms following the injection of large doses of digitoxin, and these symptoms appear to overshadow the cardiac action. The phenomena have not been investigated by us, but it was observed that slight stimuli, such as are induced by a sudden noise, or touching the cage, were followed by violent strychnin-like reflexes, and clonic convulsions which gradually subsided. Later the convulsions were absent, but a slight stimulus gave rise to violent trembling. These symptoms are present in a mild degree in the rabbit after large doses of digitoxin.

The action of digitoxin is more persistent than that of other principles of this group, and since its action persists for only a few days in the dog it seemed to be hardly worth while to test the more rapidly eliminated digitalins on that animal.

I believe that the cat behaves more like man toward the digitalins than does any other animal which is available for these experiments; hence the cat has been used in much the larger number of my experiments.

The results obtained in these experiments on cats and dogs are given in Tables 1 to 7; the experiments on rabbits will be considered later.

In these tables the initial dose, the dose required to cause the death of the animal after the interval of time following the initial dose, and the persistence of action are all expressed in percentages of the average fatal dose for the normal animal.

As previously stated, the figure which expresses the persistence of action is gotten by subtracting the figure representing the dose required after the interval following the initial dose, from 100 per cent. Thus the first animal of the first series of Table 1 required 83 per cent. of the average fatal dose for a normal animal to cause death after an interval of one day after the initial dose; hence the persistence of action in that case was equal to 17 per cent. of the average fatal dose for a normal animal of that size.

The arrangement used in the tables is intended to facilitate the study of the results obtained, for it would be necessary for the reader to consider such doses as 0.1 mg., 575 mg. and 70 mg., if actual doses were given expressed in mg. per kg. of weight.

The fatal intravenous dose of each of the digitalins used for each of the species of animals employed in this research may be found in Table 11. These doses are expressed in mg. of the drugs per kg. of body weight of the animal, and from these doses may be calculated the dose used in any experiment, should anyone care to do so.

Ouabain was used in freshly prepared solution in the final test of the persistence of action, as previously stated, in most of the experiments and where it was not used the fact is stated in a footnote.

TABLE 1.—PERSISTENCE OF DIGITALIS ACTION IN CATS

Experi- ment	Initial Dose Per Cent. of Fatal	Dose Required After Interval	Persistence of Action Per Cent. of Fatal	Interval in Days
SERIES 1				
1-B	50	83	17	1
2-B	50	56	44	2
3-B	50	50	50	3
4-B	50	54	46	4
5-B	50	110	—10	7
6-B	50	75	25	7
7-B	16.5×2	81	19	4
8-B	16.5×2	77	23	9
9-B	16.5×2	79	21	21
10-B	40	92	8	29
SERIES 2				
39	96	115	—15	28
40	108	74	26	29
43	100	32	68	11
44	100	42	58	11
49	100	52	48	10
50	100	77	23	9
SERIES 3				
4	45	62	38	33
5	45	45	55	34
6	40	117	—17	33
7	40	76	24	33
15	45	64*	36	9
16	45	76*	24	9
35	60	122	—22	14
36	84	73	27	12
37	60	84	16	28
38	60	88	12	28
SERIES 4				
1-S	75	51	49	30
2-S	75	77	23	30
3-S	75	81	19	21
4-S	75	68	32	21
5-S	75	67	33	10
6-S	75	91	9	5
7-S	75	67	33	5
8-S	75	38	62	5

*Digitalis used for final test.

DISCUSSION OF TABLE I.

The scheme of tabulation used here was not intended at the time the experiments were made, hence the numbers assigned to the experiments are not in sequence. Some of the animals died during the interval following the initial dose, as in series 2, in which six of the twelve died. The initial dose in these twelve experiments was intended to be as nearly fatal as possible without actually killing the animals.

The animals used in experiments 7-B to 9-B received two initial doses, each being 16.5 per cent. of the fatal, on two successive days, and in those experiments the intervals are reckoned from the dates of the first doses.

Some animals required more than 100 per cent. of the average fatal dose after the specified interval of time, such animals being tolerant, while in some other cases the amount required to cause death is quite as far below the amount which we would expect as those just cited are above it. Such individual differences are always seen in biological testings, but Experiments 4 and 5 of the third series require individual consideration. In both of these cases the animals were either very susceptible, or there was some error in technic.

Aside from the examples just mentioned there are great irregularities to be observed in the doses required to cause death after the intervals of time following the initial doses, and this is to be expected in view of the fact that there are two interacting causes of these irregularities.

Since these figures will receive the closest scrutiny and possibly the severest criticism, it will be worth while to discuss them here briefly.

In Experiment 1-S of the fourth series the animal required only 51 per cent. of the average fatal dose after an interval of thirty days following an initial dose reckoned at 75 per cent. of the fatal, and in 6-S of the same series 91 per cent. of the average fatal dose was required to cause death after an interval of only five days following an initial dose of the same amount as that received by the animal previously mentioned.

Such discrepancies appear at first glance to render the results almost useless, but a simple calculation will suffice to show that a comparatively slight difference in susceptibility on the part of one animal, and of tolerance on the part of the other, will explain even these great variations from the average.

If we suppose that the first of these two animals was susceptible to such a degree that it would require 20 per cent. less than the average fatal dose to cause death (and it could not have been much more susceptible, because it survived 75 per cent. of the average fatal), we shall have the following equation for this experiment:

Fatal dose, 80 mg. per kg.: initial dose ($75 \div 80 =$) 94 per cent. of the fatal; dose required after interval ($51 \div 80 =$) 64 per cent. of fatal, leaving persistence of action equal to 36 per cent. of fatal.

This would not be far from what we might expect in case the elimination was slower than normal in this animal. In the same way we may explain the unusually slight degree of persistence of action in the case of the other animal. If we suppose that this animal was tolerant to such a degree that it would require 20 per cent. more than the average fatal dose to cause death, we would then have the following equation:

Fatal dose, 120 mg. per kg. of body-weight; initial dose ($75 \div 120 =$) 62.5 per cent. of fatal; dose required after interval ($91 \div 120 =$) 76 per cent. of fatal, leaving persistence of action equal to 24 per cent. of fatal.

This would be far nearer the amount which we should expect than that shown in the table.

It was found after completion of the experiments that intervals of three weeks and more were too long except when they followed the very largest initial doses, because they prolong the average of the duration of action unduly when they follow doses smaller than those which the animal just survives.

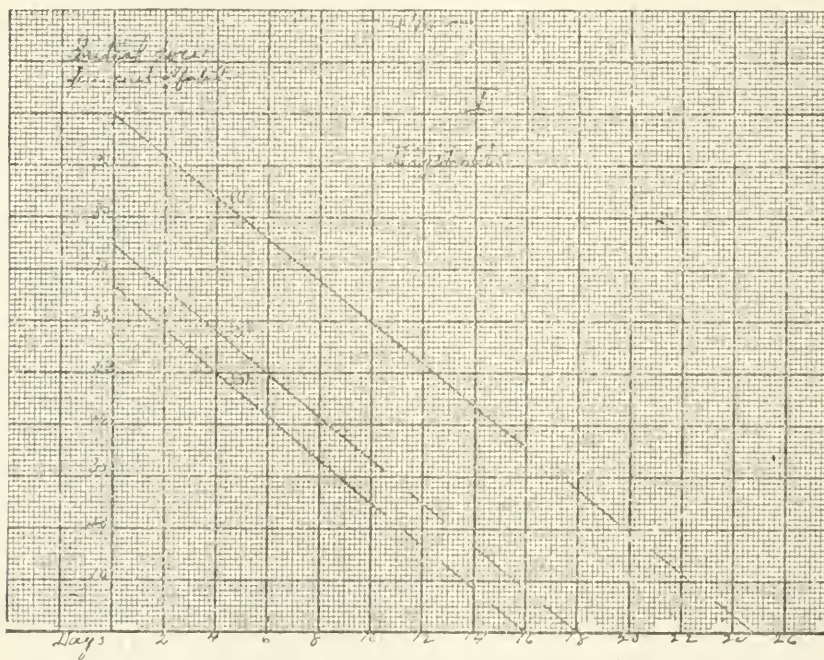


Diagram 1.—Showing persistence of action of digitalis. Upper line based on experiments in Series 2 of Table 1; middle line based on six experiments in Series 4, Table 1; lower line based on all experiments in Series 2, and all others in Table 1, except those in which interval is four weeks or more.

Reference to the several tables will show that the cat, dog and rabbit, manifest the persistence of action of digitoxin in the order of their susceptibility, as illustrated in Diagram 6, and I have gained the impression that individuals of the same species exhibit a similar relationship between these factors, the more tolerant individuals seeming to show less persistence of action after similar intervals than the more susceptible after doses which are relatively equal so far as one can judge by objective symptoms. (See discussion of Table 6.)

The averages of the results of the experiments given in several of the tables are shown diagrammatically. In these diagrams the unbroken lines indicate the decline of the action between the initial doses and the time of the final tests, and they are then continued as broken lines. While it is very probable that the elimination should be represented more accurately by curves, I have no data for the construction of such curves.

Eight of the ten experiments in the first series of Table 1 give the following averages: The initial dose was 45 per cent. of the fatal; the interval was about four days, and the persistence of action was equal to about 27 per cent. of the fatal. The entire series gives an interval of nine days, with persistence of action equal to 25 per cent. of the fatal, indicating a persistence of action far beyond that which we should expect with such doses.

TABLE 2.—PERSISTENCE OF DIGITOXIN ACTION IN CATS

Experi- ment	Initial Dose Per Cent. of Fatal*	Dose Required After Interval	Persistence of Action Per Cent. of Fatal	Interval in Days
SERIES 1				
2	50	45	55	5
3	50	48	52	5
4	50	71	29	10
5	50	75	25	10
20	66	33	67	6
21	50	76	24	15
22	50	90	10	14
23	33	88	12	14
24	33	78	22	14
25	33	70	30	14
SERIES 2				
1-D	60	66	34	1
2-D	100	37	63	2
3-D	60	71	29	8
4-D	60	40	60	7
5-D	80	26	74	4

*The fatal dose of the specimen of digitoxin used in the first series was 0.3 mg. per kg. of body-weight; that of the specimen used in the second series was 0.5 mg. per kg.

The initial dose in the second series of experiments is reckoned at 100 per cent. of the average fatal, but, as previously stated, six of the twelve animals intended for this series died, and those which survived were slightly tolerant; hence the persistence shown is less than we should expect with such doses. After deducting the 15 per cent. excess of the usual fatal dose, taken by animal No. 1, we have an average of 36 per cent. of the fatal dose persisting after an average interval of sixteen days. (Line 1 of Diagram 1.)

There are only four experiments in the third series which should be included in the results because the intervals in the others were too long. For the same reason only six of the experiments in the fourth series should be included in the calculations. These six give an average persistence of action equal to 31 per cent. of the fatal dose after an average interval of eleven days. (Line 2, Diagram 1.)

Taking all of the experiments in Series 2, and all of the remaining in the table in which the interval is less than four weeks, we have a total of twenty-five experiments with an average persistence of action equal to 23 per cent. of the fatal with an interval of eleven days following an average initial dose equal to 67 per cent. of the fatal, (line 3, Diagram 1). The nearly parallel lines of this diagram afford strong evidence that the results are approximately correct.



Diagram 2.—Showing persistence of action of digitoxin. Upper line based on all the experiments in Table 2; lower line based on five experiments with nearly equal dosage and intervals before the final test.

It is not necessary to call attention to every experiment in which the results are not in strict agreement with the general average, but it will be seen at once that four of the animals—2, 3, 20 and 25 of the first series in Table 2—were distinctly susceptible, since they required less in the initial and final doses combined than the average fatal dose. These four experiments prolong the average persistence of the series unduly, but, on the other hand, the first and second animals in Series 2, were just as certainly tolerant; hence the average persistence of this series would be shorter than it should be, and it is believed that the line (1) in Diagram 2 representing the entire number of experiments, sixteen, is very nearly a correct representation of the persistence of action of digitoxin in the cat.

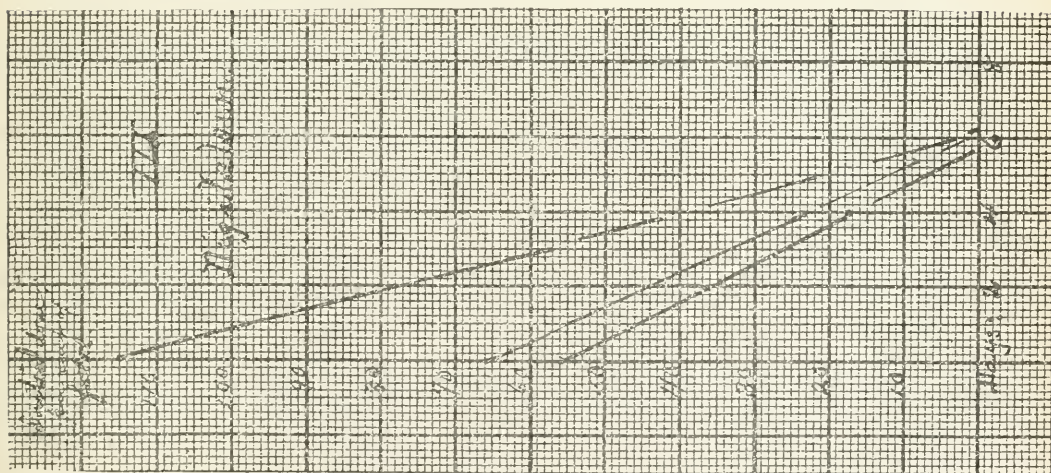


Diagram 3.—Showing the persistence of action of digitalein. Upper line based on all experiments in Table 3; middle line based on experiments in Series 2 of Table 3; lower line based on four experiments with nearly equal doses and a uniform interval of time before final test.

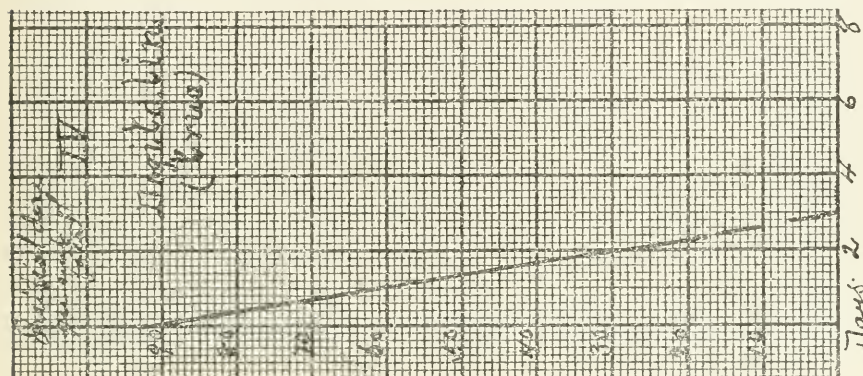


Diagram 4.—Showing persistence of action of true digitalin, based on all experiments in Table 4.

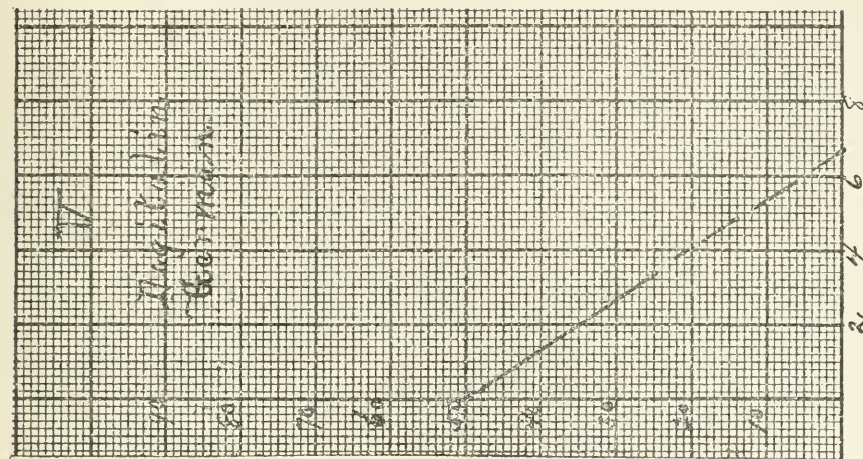


Diagram 5.—Showing persistence of action of German digitalin, based on six experiments with uniform dosage. (See Table 6.)

Line 2 in the diagram, representing the five animals with nearly uniform initial dosage and practically uniform intervals of fourteen days (one fifteen days), is nearly parallel with line 1. None of the fifteen animals failed to show the persistence of action.

TABLE 3.—PERSISTENCE OF DIGITALEIN ACTION IN CATS

Experiment	Initial Dose Per Cent. of Fatal	Dose Required After Interval	Persistence of Action Per Cent. of Fatal	Interval in Days
SERIES 1				
26	60	102	— 2	1
27	30	76	24	1
28	50	84	16	1
29	45	96	4	2
30	45	90	10	4
31	60	71	29	1
32	60	83	17	4
32a	60	67	33	2
32b	60	86	14	2
32c	60	86	14	4
32d	60	69	31	4
32e	60	110	—10	14
32f	60	86	14	14
SERIES 2				
32g	45×3*	37	63	3
32h	45×3*	29	71	3
32i	45×3*	56	44	3

*Three initial doses of 45 per cent. of the fatal were given on three successive days in these three experiments, the final test being made on the fourth day.

TABLE 4.—PERSISTENCE OF ACTION OF DIGITALIN (TRUE) IN CATS

Experiment	Initial Dose Per Cent. of Fatal	Dose Required After Interval	Persistence of Action Per Cent. of Fatal	Interval in Days
17	50×2	55	45	2
18	50×2	131	—31	2
20	66	88	12	2
21	66	82	18	2
22	50×2+33	65	35	3
23	33×3	74	26	3

The persistence of digitalein action is shown to be brief in the experiments tabulated here, hence those experiments in which the interval was fourteen days should not be included in the calculation; it will be observed, however, that the sum of the combined doses required by these two animals divided by two gives 98 per cent. of the average fatal, as we should expect after the action of the initial dose had ceased.

Diagram 3 shows a close parallelism between the three lines, (1) based on the averages of all of the experiments in both series; (2) that based on the three experiments in the second series; and (3) that based on the four experiments in which nearly equal doses were given, and a uniform period of four days was allowed to elapse before the final tests were made.

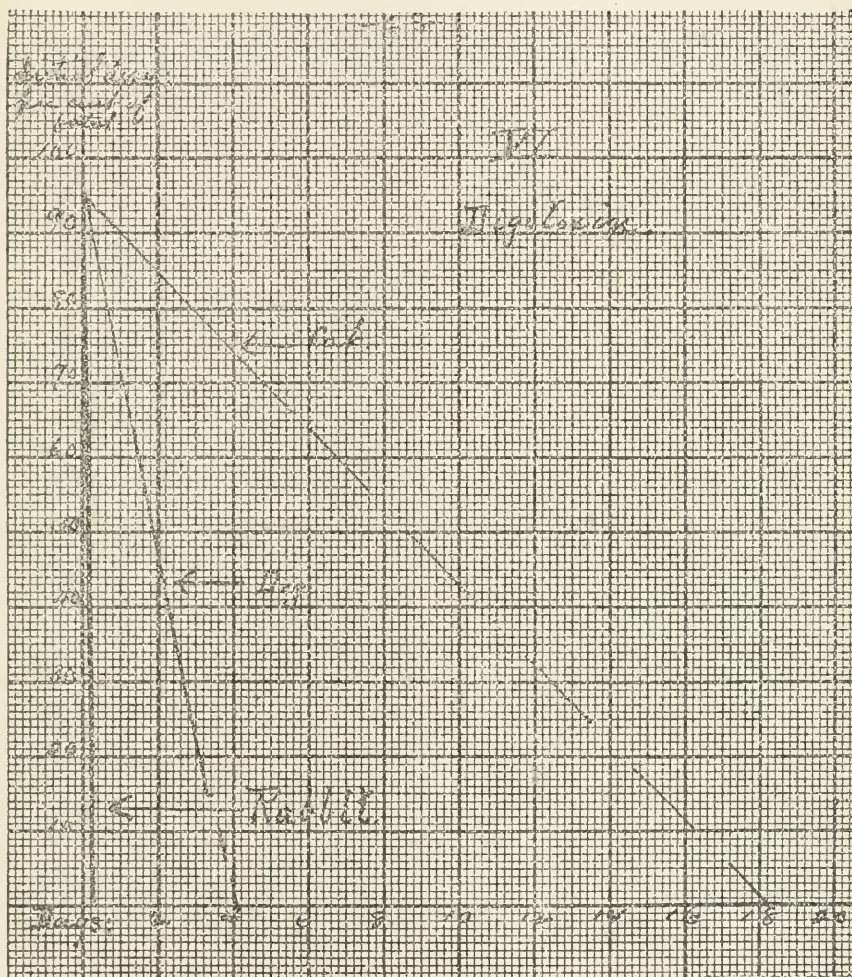


Diagram 6.—Showing persistence of action of digitoxin, on the cat (upper line), dog (middle line), and rabbit (nearly perpendicular line).

The diagrams representing the results obtained with German digitalin, true digitalin and digitalein are placed together for convenience of comparison.

Two initial doses of 50 per cent. of the fatal were given on successive days in Experiments 17 and 18, and three initial doses were given on successive days in Experiments 22 and 23, and in all four experiments the final test was made on the day following the last initial dose.

In Experiments 20 and 21 a single initial dose was given and the final test was made after an interval of two days.

The averages of the six experiments in Table 4 are as follows:

Initial dose 94 per cent. of the fatal; dose required after an average interval of two and one third days, equal to 82 per cent. of fatal, leaving a persistence of action equal to 18 per cent. of the average fatal.

The averages are represented in Diagram 4.

TABLE 5.—PERSISTENCE OF ACTION CRYSTALLINE OUABAIN AND STROPHANTHUS IN CAT

Experi- ment	Initial Dose Per Cent. of Fatal	Dose Required After Interval	Persistence of Action Per Cent. of Fatal	Interval in Days
CRYSTALLINE OUABAIN				
1	75	85	15	1
2	75	59	41	1
3	75	93	7	1
4	75	54	46	1
5	80	90	10	1
STROPHANTHUS				
1	70	69	31	1
2	55	42	58	1
3	60	56	44	1
4	60	83	17	1
5	75	92	8	1
6	75	107	— 7	1
7	75	80	20	1
8	75	70	30	1

Fraenkel⁴ found that digitalin possessed very little of the so-called cumulative action, and this agrees very well with my own results, which are shown in a striking way in the diagram.

Ouabain, strophanthin (which is methyl-ouabain) and strophanthus are generally supposed to exhibit the cumulative action to a slight degree only, or not at all.

All but one of the animals in the thirteen experiments recorded in Table 5 show some persistence of action after an interval of one day. One of the animals (No. 2 of the second series) was evidently unusually susceptible, and one (No. 6 of this series) is just as obviously tolerant, but the averages afforded by the experiments show that these drugs belong in the class with true digitalin, so far as the persistence of action is concerned.

TABLE 6.—PERSISTENCE OF ACTION OF VARIOUS DIGITALINS IN CATS

Experi- ment	Initial of Fatal Per Cent. Dose	Dose Interval After Required	Persistence of Fatal Per Cent. of Action	Interval in Days
CONVALLARIA				
40	60	99	1	3
41	75	72	28	1
42	75	92	8	1
43	70	57	43	1
44	75	94	6	1
APOCYNUM				
14	75	94	6	1
15	75	60	40	1
16	75	95	6	4
17	50	86	14	1
18	40	98	2	1
19	50×2	75	25	3
GERMAN DIGITALIN				
16	50	37	63	3
17	50	100	0	3
18	50	47	53	1
19	50	86	14	2
20	50	114	—14	3
22	50	66	34	9
SQUILL				
13	70	80	20	1
14	50×3	54	46	3
15	50×3	30	70	3
16	50×3	42	58	3
17	80	57	43	2
18	80	71	29	2
BLACK HELLEBORE				
11	50	94	6	1
12	50×2*
13	50×3*
14	50×3	29	71	3
15	80	47	53	2
16	80	51	49	2
17	80	46	54	2
HELLEBOREIN				
7	50	65	35	1
8	50×3*
9	50×3*
10	80	36	64	2

*Fatal.

Experi- ment	Initial of Fatal Per Cent. Dose	Dose Interval After Required	Persistence of Fatal Per Cent. of Action	Interval in Days
CONVALLAMARIN				
8	44	64	36	1
9	70	68	32	2
10	70	74	26	2
11	45+50	73	27	2
12	45+50+50	39	61	3
12 [†]	80	89	11	2
14	80	73	27	2
SCILLITOXIN				
7	70	70	30	3
8	80	60	40	3
9	70+50+50	60	40	7
10	70+50+50	35	65	7
11	50+50+50 [†]
12	50+50+50	22	78	3
EUONYMUS				
7	50	102	— 2 ~	1
8	50	87	13	1
9	50×2	54	46	2
10	50×2	44	56	2
ADONIDIN				
8	58+58 [†]
9	58+58+58	42	58	3
10	80+60	27	73	4

[†]Suddenly fatal.

The experiments furnish the following averages:

Crystalline ouabain, initial dose, 76 per cent. of fatal; persistence of action after an interval of one day equal to 24 per cent. of the fatal; strophanthus, initial dose, 68 per cent. of fatal; persistence of action after an interval of one day equal to 25 per cent. of the fatal.

In several of the experiments in Table 6 the animals received more than one initial dose; in such cases these were given on successive days, except in the case of scillitoxin, in which the initial doses were given at intervals of two days. In all cases the interval before the final test is reckoned from the date of the first initial dose.

German digitalin is said to consist of digitonin to a very large extent, and the action of digitonin on the heart is not quite like that of true digitalin, so that it is not surprising that the results obtained with this preparation are not very satisfactory. The similarity of action to that of digitalein is to be noted.

Digitalis also contains digitonin, but the amount present in the leaf is said to be small, and it should be remembered that the cardiac action

of digitonin is not obtained after the oral administration of digitalis or the other digitalins. The final test was made with the same drug which was used for the initial dose in every experiment recorded in Table 6. but we had found that all of these digitalis bodies are synergists of ouabain.

The digitoxin was administered intramuscularly in Experiments 1 to 9 inclusive, and intravenously in the others.

TABLE 7.—PERSISTENCE OF DIGITONIN ACTION IN DOGS

Experi- ment	Initial Dose Per Cent. of Fatal	Dose Required After Interval	Persistence of Action Per Cent. of Fatal	Interval in Days
1	95	60	40	3
2	60	100	00	11
4	95	100	00	2
5	80	75	25	9
7	95	100	00	5
9	95	100	00	9
10	95	77	23	1
11	95	67	33	1
12	80	100	00	3
13	95	100	00	3

TABLE 8.—DIGITALIS IN REPEATED DOSES TO RABBITS INTRAVENOUSLY

(Doses in milligrams per kilogram of body-weight)

DAYS												
Exper:	1	2	3	4	5	6	7	8	9	10	11	Total
1	50	67	...	100	100	...	200	...	200	...	300	*1,017
2	100	...	100	100	...	200	...	200	...	200	250	1,150
3	165	...	200	...	200	...	200	250	200	1,215
4	160	...	200	250	250	200	350	300	1,710
5	170	...	200	...	200	...	200	250	250	500	300	2,070
6	200	200	400
7	200	200*	400
8	200	250	250	700
9	200	200	...	200	250*	850
10	200	200	250*	650
11	400†	400

* Fatal. † Two doses at intervals of three hours. fatal.

It is evident that dogs do not usually show persistence of digitoxin action for long periods, and of the eight experiments in which the duration of the interval was more than a day, only two, (1 and 5,) show any persistence of action. That the action did actually persist in these two cases is rendered more probable by the fact that the first of these animals, which shows persistence of action amounting to 40 per cent. of the fatal after three days, was greatly depressed for two days following the first dose, and the other animal, which shows persistence of action equal to 25

per cent. of the fatal, had lost 1.5 kg. of body-weight during the interval. The weight at the time of the first injection was 12.5 kg., and at the time of the final test the weight was 11 kg.

Here again the attention is arrested by the question whether individual differences in tolerance and susceptibility stand in any sort of relation to differences in the individual capacity for elimination, as suggested in the discussion of Table 1.

In the fourth and fifth experiments the animals received two doses each on the tenth day. Two hundred and fifty mg. of digitalis per kg. of body-weight appears to be the average fatal intravenous dose for the rabbit, but two rabbits survived doses of 300 mg. per kg. each, and one of these, No. 5, had had two doses of 250 mg. per kg. each on the previous day.

TABLE 9.—EFFECT OF DIGITONIN IN REPEATED DOSES TO RABBITS BY VEIN

(Doses are given in milligrams per kilogram of weight)

Exper.	DAYS								Total
	1	2	3	4	5	6	7	8	
1	0.75	0.5	0.75	2.0
2	0.5	0.5	0.5	0.5	0.5	0.75	3.25
3	0.5	0.5	0.5	0.5	0.75	*2.75
4	0.75	1.5	1.5	*3.75
5	0.5	0.75	0.75	0.75	0.75	3.5
6	0.75	0.75	0.75	0.75	0.75	3.75
7	0.5	0.75	0.75	0.75	0.75	0.75	0.75	†7.0

* Fatal † 1.0 milligram on tenth day and 1.0 mg. on twelfth day.

The eleven rabbits weighed 18.41 kg., they received a total of 19,000 mg. of digitalis during a total of seventy days of experimentation, or an average of less than a week for each animal, but even this stupendous amount does not represent the limits of dosage for this animal; but its capacity for eliminating the digitalins was not suspected at the time the experiments were conducted.

In this connection it must be remembered that the amounts administered to these rabbits correspond to very much larger amounts administered by the stomach, or subcutaneously.

The fourth animal of this series died of respiratory failure. The seven rabbits received an average total of more than 3.5 mg. of digitonin per kg. during the entire period.

Impressive as the figures for this and the preceding table are, they lose much of their significance in view of the results recorded in Table 10, in which it is shown that the rabbit eliminates digitonin with surprising rapidity.

The following is the protocol of an experiment which shows that the rabbit exhibits no persistence of action of digitoxin after an interval of a few hours following the intravenous administration of a nearly fatal dose.

May 29, 1912: Rabbit, weight, 1.7 kg.
 8:41 a. m. 1.0 mg. digitoxin per kg. by vein; some depression.
 9:41 a. m. Animal sitting up.
 12:56 p. m. 1.0 mg. digitoxin per kg. as before.
 1:10 p. m. Effects about the same as after previous dose.
 1:56 p. m. Appears to be nearly normal.
 2:56 p. m. Ouabain, slow and continuous injection by vein.
 3:34 p. m. Death after injection of 0.19 mg. ouabain per kg., or the full fatal dose of ouabain.

TABLE 10.—PERSISTENCE OF ACTION OF DIGITOXIN IN THE RABBIT
 (Doses in mg. per kg. of body-weight)

Initial Dose of Digitoxin	Dose Required After Interval	Interval in Hours	Persistence of Action
4.0 (subcut.)	0.206 ouabain	26	00
0.75 (vein)	0.245 ouabain	4.5	00
0.75 (vein)	0.212 ouabain	4.5	00
2.0 (vein)	0.19 ouabain	*	00

* See protocol.

I believe that hitherto no one has suspected that the rabbit is capable of eliminating digitalis and digitoxin with the extraordinary rapidity indicated in Tables 8, 9 and 10, and as shown in the protocol of the experiment. Certainly no one has ever before recorded the administration of digitoxin in such amounts and at such short intervals during studies of this nature, for it must be remembered that the subcutaneous and oral administration are in no way comparable to the intravenous injection of this principle, because of the slow and uncertain absorption from the gastro-intestinal tract and from the subcutaneous tissues of the rabbit. (See Experiment 1, Table 10.)

It is hardly necessary, therefore, to call attention to the fact that previous studies of cumulation, so-called, based on the oral or subcutaneous administration of the digitalins to rabbits lose much of their value because it is obvious that absorption is a more important factor in the results so obtained than is the persistence of action which follows the absorption into the blood-stream of the drugs so administered.

It will be understood that the doses given in Table 11 apply only to the specimens of the drugs used by us in these experiments, but crystalline ouabain appears to be of constant composition and activity.

The fluid extracts used were obtained from a reputable firm, but it is probable that they do not represent the full activity of the drugs from which they were prepared. The tincture of digitalis used was prepared in this laboratory, care being taken to insure the complete exhaustion of the drug.

TABLE 11.—FATAL DOSES OF DIGITALINS BY VEIN IN MILLIGRAMS PER KILOGRAM OF BODY-WEIGHT

CAT	
Ouabain (crystalline strophanthin, so called)	0.1
Digitoxin (specimen used in Series 1, Table 2)	0.3
Digitoxin (specimen used in Series 2, Table 2)	0.5
Scillitoxin	0.4
Digitalin (true)	1.5
Helleborein	1.7
Convallamarin	1.7
Digitalin	3.5
Digitalin, German	3.6
Adonidin	4.35
Convallaria (fluid extract used)	50.0
Apocynum (fluid extract used)	70.0
Digitalis (tincture prepared by ourselves)	100.00
Black hellebore (fluid extract)	100.00
Euonymus (fluid extract)	475.0
Squill (fluid extract used)	575.0
DOG	
Ouabain	0.125 to 0.175
Digitoxin (specimen used in Series 1, Table 2)	0.5
Digitalis	125.0
RABBIT *	
Ouabain	0.2
Digitoxin (specimen used in Series 1, Table 2)	0.75 to 1.0
Digitoxin (specimen used in Series 2, Table 2)	1.0 to 1.5
Digitalis	200.0 to 250.0

* The doses given are for rabbits weighing about 1,800 gm. or less; fully grown rabbits appear to be slightly more susceptible than this to the digitalins.

Reference to the table suggests some curious relationships between several of the digitalins; for example, digitoxin and scillitoxin are about equal in activity and their persistence of action is not widely different; true digitalin, helleborein and convallamarin are almost exactly alike in activity, and none of these three shows a markedly persistent action. German digitalin and digitalin are about equal in activity, and we know that both of these partake of the nature of true digitalin on the one hand, and of digitonin on the other.¹⁰

Too much stress should not be placed on similarities in activity of the digitalins, however, since none of these bodies except ouabain is found in commerce in a pure form. Ouabain appears to have only traces of impurities present.

ANALYSIS OF CERTAIN RESULTS OF FRAENKEL'S

Reference has been made to the fact that Fraenkel's conclusions based on results obtained when using digitalins on the cat are irreconcilable with mine. It is necessary, therefore, to discuss some of his experiments

10. Schmiedeberg: Arch. f. exper. Path. u. Pharm., 1875, iii, 16.

which, interpreted correctly, actually confirm my own results in all essentials, I believe.

Fraenkel⁴ fixed the fatal dose of Merck's crystalline digitoxin for the cat by subcutaneous injection at 0.08 mg. per kg. of body-weight and then he administered specified fractional parts of this dose daily, observing the onset and severity of the gastro-intestinal symptoms, the effects on the heart and pulse-rate and the number of such doses that the animal would survive, comparing the effects of digitoxin with those of the other digitalins in common use, including digitalin and strophanthin.

TABLE 12.—EFFECT OF DIGITOXIN ON CATS

(Taken from article by Fraenkel⁴)

Experiment:	Digitoxin Given	After How Many Days	After How Many Doses Vomiting?	After How Many Doses Sick?	Remarks
.....	Per Kg.
.....
.....	Slowing?	ing?
40	22 x 0.02	5	Not seen.	Not seen.	Remained sound.
9	9 x 0.03	2	3	9	Stopped; Animal very sick.
20	2 x 0.04	2	Not seen.	Not seen.	Remained sound.
44	16 x 0.04	4	6	6	Death after 16 doses.
11	5 x 0.041	3	5	5	Stopped after 5 doses; very sick.
8	7 x 0.05	3-4	3-4	4	Death after 7 doses.
10	7 x 0.087	1	2	3	Death after 7 doses.

It will be seen by reference to Table 12, which is taken from Fraenkel's article, that several of his cats survived a total of much more than the amount which Fraenkel gives as the single fatal dose; thus, one of his animals is stated to have received sixteen daily doses, each of which was 50 per cent. of the fatal, or a total amount equal to eight times the single fatal dose within a period of fifteen days; another survived three times the fatal single dose, administered in five days; while two required to cause death amounts equal to four and seven, times the fatal dose, respectively, within a period of a week.

If these conclusions were correct it would show that the action of digitoxin is not very persistent when used in that way, but while Fraenkel does not state specifically the number of experiments which he made to determine the toxicity of digitoxin for the cat, he gives the protocol of only one experiment and in that the animal died on the tenth day after the injection.

No less than five observers working independently in this laboratory at different times have been unable to confirm Fraenkel's determination of the fatal dose of digitoxin for the cat.

Bailey, Brody, Eggleston, Mr. M. I. Smith (one of my students), and I have found that the fatal dose of different samples of Merck's crystalline digitoxin is much larger than that given by Fraenkel.

Bailey found that doses of 0.1 mg., and 0.2 mg., per kg. of body-weight injected subcutaneously, produced very little effect on the pulse-rate of the cat, and, in fact, little or no perceptible effect of any sort was produced by these doses administered to two animals.

Hatcher and Brody,⁹ Eggleston, and later I, while repeating the work, have found that the fatal intravenous dose of several different samples of Merck's crystalline digitoxin for the cat is approximately 0.3 mg. to 0.35 mg. per kg. of body-weight, and I have found the fatal dose for the cat by subcutaneous injection to be somewhat larger than that by vein, as one might expect. I have quite recently found a specimen of Merck's digitoxin obtained from another firm, and not bearing Merck's label, to have only about 60 per cent. of the activity of the specimens previously examined. (This is the weaker specimen mentioned in Table 11.)

If we accept 0.4 mg. of digitoxin per kg. of body-weight as the average fatal dose for the cat by subcutaneous injection, it will be seen that Fraenkel's results, so far from being irreconcilable with my own, afford strong corroborative evidence of the persistence of action in the cat.

If the fatal dose of digitoxin used by Fraenkel was really 0.4 mg. per kg. when administered subcutaneously, his animals received only a little more than the single fatal dose within a period of a week, and instead of receiving totals of three, four, seven and eight, times the single fatal dose, respectively, they received totals of three-fifths (this animal survived), one, one and a half, and one and three-fifths times the single fatal dose, from which the last three died.

One might argue that the specimen of Merck's crystalline digitoxin used by Fraenkel was far more active than the specimens used in this laboratory, and I am well aware that it is commonly stated that the activity of different specimens of all of the digitalis principles varies widely, but while the activity of a given principle made by different manufacturers may show great variations, and the product made at different times by the same manufacturer may vary somewhat, the results obtained by numerous observers indicate no very great variation in the activity of Merck's crystalline digitoxin.

Among those who have determined the activity of digitoxin and whose results are in fair agreement with those obtained in this laboratory (allowance being made for differences due to different methods of testing), are: Lyons and Famulener,¹¹ Worth Hale¹² and Koppe,¹³ On the other hand, I know of no one whose results confirm those of Fraenkel.

11. Lyons and Famulener: *Proc. Am. Pharm. Assn.*, 1902, 1, 424.

12. Hale, Worth: *Bull.* 74, 1911. *Hyg. Lab., U. S. Public Health and Marine-Hospital Service.*

13. Koppe: *Arch. f. exper. Path. u. Pharmacol.*, 1875, iii, 274.

If the digitoxin used by Fraenkel behaved in the way indicated by him it means that the specimen of Merck's digitoxin employed by him is far more active than any which has been used in experimentation in this country, and furthermore, that its behavior is much more like that of ouabain, so far as persistence of action is concerned, than like that of digitalis.

No other worker either in Europe or America has ever reported such activity for digitoxin on mammals as Fraenkel has reported in this series of experiments, so far as I am aware, and I believe that Fraenkel's results with repeated injections disprove his own statement as to the lethal dose of this drug, if by lethal dose we are to understand the amount which will kill at least half of the animals in a series through the action on the heart.

There is little doubt that when an animal is made ill by the injection of one of the digitalins it is more apt to succumb to more or less accidental conditions during a prolonged confinement than is a normal animal, and I believe it to be wholly erroneous to attribute all the deaths which occur in ten days or more after the administration of a single dose of the digitalins to the cardiac action of the drug.

It might be urged that digitoxin behaves differently after subcutaneous and intravenous injections; I have, therefore, repeated Fraenkel's experiments to the extent of injecting repeated doses of less than 50 per cent. of the fatal dose subcutaneously. In these experiments the cats received: 0.6 mg. per kg. of body-weight in four days; 0.75 mg. per kg. in five days; and 0.7 mg. per kg. in three injections in six days, before death resulted. These results agree very well with those reported by Fraenkel so far as the actual amounts administered are concerned. I am therefore forced to the conclusion that the so-called fatal dose of digitoxin as determined by Fraenkel, can be fatal only under very exceptional conditions, and is of no value whatever in determining the persistence of action of digitoxin.

This misconception of the activity of digitoxin appears to have led Fraenkel into another error. He concluded that the interval of time which must elapse after a digitalis principle enters the circulation before its action on the heart is induced must be proportional to the chemical affinity existing between the drug and the tissue on which it acts, whereas the duration of the action must depend on the stability of the combination of drug and tissue.

The truth of this conclusion, based on theoretical considerations, seems self-evident; nevertheless it was based on a wholly erroneous idea, in that Fraenkel believed that the action of digitoxin on the heart was not exerted for many hours after its introduction into the blood-stream, and he states that even sixty hours may elapse after the administration of

a toxic dose before this cardiac action is induced. It is obvious that he fell into this error partly because of his erroneous belief that he was administering a highly toxic dose, when, in reality, he was administering only a small part of the fatal dose.

It is perfectly true that digitoxin does not exert its full action immediately after the injection of small amounts into the circulation, but death may result in about five minutes after injection of about twice the ordinary fatal dose of digitoxin directly into the veins of the cat or dog. When a very large dose of digitoxin is injected directly into the veins the action is induced with amazing swiftness, the heart stopping suddenly almost without warning on its part.

The belief which is well nigh universal, that digitoxin is an extraordinarily toxic substance, is based mainly on the well-known experiment in which Koppe¹³ administered to himself by the mouth three doses of digitoxin amounting altogether to 3.5 mg. in a period of five days, 2 mg. having been taken four days after the second dose of 1 mg.

Since Koppe had previously given a rabbit 4 mg. of the digitoxin subcutaneously without causing death, there is little doubt that he was extraordinarily susceptible, or that his illness following the taking of the digitoxin was due to other causes in part.

CONCLUSIONS

In presenting the results of my experiments I would not intimate a belief that the last word had been spoken concerning the persistence of action of the digitalins or the so-called cumulation of these bodies, but I do believe that my results afford a starting point for investigating the subject anew.

It is obvious that the rabbit is not suited for these studies and that the cat serves the purpose better than the dog. The injection of the digitalins directly into the circulation affords so much greater accuracy of observation than the oral and subcutaneous routes, that the former method alone should be used for these investigations.

Changes in the heart-rate of the cat and the rabbit occur so often independently of the administration of the digitalins that they afford very little information concerning the persistence of action of these drugs.

The several digitalins vary widely in their toxicity for any given species of animal, and the different species of animals show enormous differences in susceptibility to a given digitalin, but so far as I have been able to determine, as the result of a large number of experiments, the various digitalins maintain their relative positions in order of toxicity, regardless of the animal used for the determination provided that the drug is introduced directly into the circulation; but the absorption of these bodies from the gastro-intestinal tract is so variable that the effects

which follow the oral administration afford no clue to the activity which they will exert when they are injected directly into the circulation.

It remains for the clinician to determine whether it will be advantageous in a given condition to utilize the prolonged actions of digitalis and digitoxin or the briefer actions of strophanthus and digitalin, but it seems more than probable that the more persistent action will be found preferable in certain chronic cardiac conditions, whereas the less lasting digitalin action probably will be preferred in certain conditions such as acute cardiac dilatation.

It is of the first importance to the clinician to know that the various digitalins are synergistic in their action, and that when one member of the group is used in such a way that its action is elicited promptly (as after intramuscular, or intravenous injection) during the period when the action of a previously used digitalin persists, the dose of the drug so used must be regulated carefully because inattention to this detail may result disastrously.

SUMMARY

The production of the phenomena commonly called "cumulation" of the digitalins, depends on the relationships existing among a number of factors, including absorption, elimination and persistence of action, all of which are in need of investigation. The use of the term cumulation tends to perpetuate a misconception.

The actions of the digitalins persist for periods of time which vary widely with the different members of the group, and with the species of animal employed.

The actions of digitoxin and digitalis persist longer than do those of the other digitalins in common use.

The cat shows this persistence of digitalis action much longer than the dog, rabbit or white rat.

The cardiac actions of a single very large intravenous dose of digitalis or digitoxin may persist for a full month in the cat, but for only a few hours in the rabbit.

The actions of the largest sublethal dose of digitalin, ouabain or strophanthus persist for only a day, or, at most, a few days, in the cat.

It remains for the clinician to determine whether the long-lasting action of digitalis or the briefer action of strophanthus is to be preferred in a given condition of cardiac disease, but strophanthus cannot rival digitalis in general use until we learn more of the conditions governing its absorption from the gastro-intestinal tract, and of this we know practically nothing at present.

Careful regulation of the therapeutic dosage of the digitalins is necessary in order to avoid accidents. This is especially necessary when they are used in such a way that the action is elicited promptly during

the period when the action of a previously used digitalin persists, and in this connection it must be remembered that every digitalin is a synergist of every other member of the group.

All of the digitalins maintain their relative position with regard to activity, so far as we have tested them on different mammals, by intravenous injection, and digitoxin has never been found by any observer to be as active as crystalline ouabain when tested on mammals in this way; hence there is no sufficient reason for the wide-spread belief that digitoxin is enormously toxic for man, as compared with other digitalins.

No fixed ratio of activity can be determined for the digitalins when they are administered orally, because of great differences in the rate of absorption from the gastro-intestinal tract.

The full effects of moderately large doses of digitoxin are not exerted on the heart at once even when they are administered intravenously, but severe symptoms of poisoning may be elicited in a few seconds, and death may occur within two minutes, after the intravenous injection of a very large dose of digitoxin.

The rabbit eliminates certain of the digitalins, at least, with a rapidity hitherto unsuspected, and previous studies of the so-called cumulative actions of these bodies, in which they were administered orally, or subcutaneously to rabbits, lead to wholly erroneous conclusions.

Changes in the pulse-rate amounting to fifty beats per minute occur spontaneously in the cat and the rabbit, and large doses of digitalis often fail to elicit any constant changes in the pulse-rate of these animals; hence such changes as may occur after the administration of the digitalins to these animals afford no trustworthy indication of the persistence of action of the digitalins. (See protocol of experiment, p. 273.)

Further studies of the digitalins are in progress in this laboratory, among the problems under investigation being those of absorption from the gastro-intestinal tract; the rate at which the digitalins leave the blood-stream; their elimination from the organism; their storage in the tissues, and their persistence of action.

I wish to acknowledge my indebtedness to Mr. M. I. Smith, one of my students, for assistance in carrying out many of the experiments in this research.

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THE FAT METABOLISM OF LIPOMAS *

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CHICAGO

There is a widespread belief that the fats of lipomas are not available to the host as a source of reserve food-supply. This is based on certain reputed instances in which the bearer of a lipoma is said to have become greatly emaciated from some intercurrent disease, notwithstanding which the lipoma has either remained its original size or has even continued to grow. Specific cases in which such occurrences have been accurately observed and reported are, however, difficult to find.

Shattock,¹ in an interesting discussion of "Localized Fatty Deposits," has commented on this paucity of evidence. He himself knew of but two such reputed cases, and reinvestigation of some of the supposed lipomas in one of these cases showed them to be caseous lymph-nodes. Furthermore, he mentions a third case in which a subcutaneous lipoma *did* decrease in size during the emaciation of the patient. A diligent search of the literature has not revealed to me many positive observations on this point.

Askanazy² reports the presence of multiple lipomas (which he looks on as a replacement of lymph-nodes by fat, comparable to the normal involution of the thymus) in a woman who became emaciated because of a thyroid sarcoma; but he does not state whether the lipomas grew or diminished in size during the emaciation. Under the caption of "Subperitoneal Lipomata," Campbell³ reports a case in which the tumor increased in size during the progress of emaciation, but the tumor was in reality a fatty sarcoma, and hence falls outside the limits of this problem. Adami⁴ also states that in the huge retroperitoneal lipomas it is noticeable that the mass continues to grow and to enlarge at the expense of the rest of the body, while the normal fat deposits are being exhausted by the emaciating patient. This feature seems prominent in

*From the Pathological Laboratory of the University of Chicago.

¹Submitted for publication July 18, 1912.

1. Shattock: Proc. Royal Soc. Med., 1909, ii, 176.

2. Askanazy: Virchow's Arch. f. path. Anat., 1899, clviii, 408.

3. Campbell: Brit. Med. Jour., Nov. 28, 1903, p. 1397.

4. Adami: Montreal Med. Jour., 1897, xxv, 529 and 620.

most of the fatty tumors which arise in the retroperitoneal region, as is brought out in the compilation of eighty-one cases by Voeckler,⁵ most of which showed cachexia.

The nature of these tumors is somewhat uncertain — they are more cellular than ordinary lipomas, have a great tendency to myxomatous change, and resemble malignant tumors in their fatal outcome and in the tendency to recur after removal. In not a few there is an actual sarcomatous transformation of the tumor, which is especially likely to be observed in the recurrent growths, as in Voeckler's case. These tumors of the perirenal fat tissue are not exactly comparable with subcutaneous lipomas, but they do present in a conspicuous way the ability of tumors to lay up a deposit of fat which the emaciating body cannot use for its own purposes. Therefore, tumor cells can not only build up their own cellular structure of proteins which are inaccessible to the rest of the wasting body, but they can also lay on and withhold fat, which seems in all respects to resemble the normal stored food. Since normal tissues do not ordinarily store fat for their own use, but for the use of the entire organism, this holding of fat by tumor cells when the rest of the body needs it, is entirely out of harmony with normal fat metabolism and challenges explanation.

Although many of the text-books on general pathology and pathology of tumors entirely omit mention of this property of lipomas (Aschoff, Senn, Bland-Sutton, Delafield and Prudden, Beattie and Dickson, American Text-Book), yet there are several which give general statements without specific references or data. Borst⁶ states that the autonomy of lipomas is shown by the fact that when, in the course of a general emaciation, the physiologic fat depots of the body disappear, an existing lipoma will remain unaffected, or even continue to grow; further, it is also frequently observed that lipomas may develop on extremely emaciated individuals. Kaufmann⁷ says that in general emaciation of the host, lipomas do not participate, which illustrates well the independence of the tumors. Ziegler, in his *General Pathology*, says, "A complete disappearance of a lipoma does not take place in the case of extreme general emaciation of the individual."

That fat in lipomas is not necessarily unavailable to the organism is shown by certain cases in which absorption of the tumors has occurred. One of these is the case previously quoted from Shattock.¹ Most striking is the case described by Broca:⁸ A man, 31 years old, had a five-pound lipoma excised from the thigh. Five months later hundreds of small fatty tumors appeared all over the body, and persisted and developed

5. Voeckler: *Deutsch. Ztschr. f. Chir.*, 1908, xcix, 149.

6. Borst: *Die Lehre von den Geschwülsten*, i, 137.

7. Kaufmann: *Spezielle Pathologie*, 1911, ed. 6, p. 1312.

8. Quoted by Warthin, *Reference Handb. Med. Sc.*

about forty years, until the man was nearly 70 years old. He then began to suffer from dysphagia, which caused emaciation. This at first did not affect the tumors, but after several weeks the emaciation became extreme and the tumors diminished. Death finally resulted from starvation. At autopsy no trace of fat was found in the normal fat deposits. A large fatty tumor surrounded the esophagus for the greater part of the extent, occluding the lumen. Other fatty growths were found in many places. Many of the tumors had lost their fat and consisted of fibrous tissue; the others presented the appearance of fibrolipomata. The classification of such a tumor, with sudden dissemination like a cancer, but of essentially benign course, is a difficult matter, and this uncertainty makes the true significance of this remarkable case questionable.

Baker⁹ reports a case in which multiple cervical lipomas became reduced in size (to one-half or one-third their original size) during a period of emaciation brought about by some obscure lung disease, increasing in size again later. Unfortunately the report lacks many details necessary to carry conviction as to the fatty nature of the tumors. According to the statistics of Madelung,¹⁰ the diffuse fatty tumors of the neck are characterized by independence from the general body condition. He himself observed a case in which emaciation of the patient from pulmonary disease had no effect on the growth in the neck. Of the cases in the literature collected by him, some of the patients were well nourished, none obese, some were thin or even emaciated. Of these, Kuster's case showed a cessation of growth in the lipoma when the patient became emaciated (from "gastric disorder"), but the lipoma did not diminish in size.

It is indeed difficult to understand how the fat of a lipoma can exist as it does, in intimate relation to the blood-vessels, and not be utilized when the host needs fat. We know of no anatomic peculiarity that can explain such anomalous deportment on the part of the fatty areolar tissue of lipomas. As Shattock has emphasized, the lipomas are structurally comparable to certain normal localized fat deposits, e. g., the "hump" of the dromedaries, the fat-tailed sheep, the steatopygous masses of Hottentots, etc., yet all these deposits are drawn on when needed for nutriment. The camel starts off on a journey across the desert with full and erect humps and reaches its destination with the humps reduced to pendant, flabby bags of skin. On the other hand, more comparable with the reputed behavior of lipomas, are the sucking cushions in the cheeks of infants, which persist during emaciation.

9. Baker: *Tr. Path. Soc.*, London, 1879, xxx, 417.

10. Madelung: *Arch. f. klin. Chir.*, 1888, xxxvii, 106.

CHEMISTRY OF NORMAL AND LIPOMA FAT

A chemical difference between the lipoma fat and the fat of the normal fat depots might explain this unavailability of lipoma fat, but no such difference, of sufficient magnitude to be revealed by existing chemical methods, has been found. The careful study of lipoma fat by Jaeckle¹¹ showed a remarkably close resemblance to normal subcutaneous human fat. In the fatty masses of adiposis dolorosa Edsall¹² found the fat quite similar to normal fat.

Failing adequate explanation by structure or chemical composition, it might be imagined that there is a deficiency or abnormality of the enzymes of fat metabolism in the connective tissues. This possibility has not been investigated previously. According to the investigations of fat metabolism by Kastle and Loevenhart, the storage of fat by tissues depends on the presence in these tissues of the enzyme lipase, which acts reversibly, either to split fat into fatty acids or glycerin, or to synthesize fat from these diffusible constituents as they are provided by the blood; the direction of the reaction depending on the conditions of equilibrium. One might imagine that absence of lipase from lipomas might account for the inability of the fats to be rendered available to the body; however, in this case the storage of the fat in the lipoma would be difficult to explain. Bearing on this hypothesis is the observation of Loevenhart,¹³ that watery extracts which he prepared from the retroperitoneal and pericardial fat had less lipolytic activity than extracts from subcutaneous fats, and that the two former fats are absorbed less rapidly during emaciation than are the subcutaneous fats.

We have tested the lipolytic activity of a number of lipomas kindly supplied us by surgical friends, and also specimens of human fat tissue. At first attempts were made to observe autolipolysis of the fatty tissues, by contrasting the development of acids in fresh fatty tissue or lipomas with boiled portions of the same specimens. These experiments all failed, because the antiseptics (toluene, chloroform) are taken up to such an extent by the fats that putrefaction occurs even in the presence of a large amount of antiseptic. We therefore were obliged to remove the fat by extracting the tissue with ether as rapidly as possible, until free from fat, then grinding and drying the extracted residue, which could then be kept until wanted. We have no means of knowing to how great an extent, if any, the lipase is injured by this proceeding, but it is not destroyed. Such extracted tissues when added to natural fats and simpler esters in watery solutions or emulsion cause marked hydrolysis, but any quantitative results obtained in such experiments are worthless. The

11. Jaeckle: *Zeitschr. f. physiol. Chem.*, 1902, xxxvi, 53.

12. Edsall: *Amer. Jour. Med. Sc.*, 1902, cxxiv, 994.

13. Loevenhart: *Am. Jour. Physiol.*, 1902, vi, 541.

proportion of stroma, blood-vessels, fascia, etc., in such tissue, the manipulations necessary in preparing the material and the unnatural conditions under which the lipolysis is carried out, must necessarily have so much influence on the results obtained with any sample of tissue that these results cannot be considered as reflecting the lipolytic activity of this tissue in its natural condition. All we can say is that our tissues as prepared are or are not possessed of thermolabile lipolytic activity. In the experiments were used natural human fat, lipoma fat, olive oil, ethyl butyrate and triacetin. The latter glycerol ester, which is recommended by Taylor,¹⁴ seems to be, as he maintains, the best for experimental study of lipolysis, because it is water soluble and yet is a triglycerid. The insoluble fats are too slowly attacked by lipase because of the small surface for action which they exhibit even when emulsionized, while such simple soluble esters as ethyl butyrate are chemically too dissimilar to the triglycerids of natural fats to make them valuable indicators of the normal lipases which split triglycerids.

EXPERIMENTS

The experiments were conducted as follows:

One-half gram of the powdered tissue was placed in 50 c.c. of water to which 2 c.c. toluene was added, and then 2 to 4 c.c. of the fat or ester was added, as indicated in the tables. The various experiments were performed at different times, and through an oversight the amounts of fats and esters used were not the same in each case. This, however, is not a matter of great importance, for the results are, as previously emphasized, qualitative only and not quantitative. Phenolphthalein was used as the indicator, and titration was made with $n/10$ NaOH and HCl, the figures given representing cubic centimeters of the $n/10$ alkali required to neutralize. Neutralization was done at various intervals, the length of which probably has some influence on the total results, for it is evident from the data given that with each tissue the amount of acid formed is not very different whether the interval is one, two, or several days, suggesting that after a certain degree of acidity is reached, there begins to be an inhibition of the hydrolysis. With all specimens, it will be noticed, there was more hydrolysis when the tissue that had been heated in boiling water for thirty minutes was present than when there was only water, indicating that there is some thermolabile agent which accelerates hydrolysis. There is, however, in every case except that of the action of the fibrosarcoma on lipoma fat and olive oil, a definite excess of hydrolysis in the presence of unboiled tissues, whether lipomas, sarcomas or normal fat tissue. There are, however, no quantitative differences which seem striking enough to be of any significance whatever under the conditions of the experiment. Usually there is considerable more hydrolysis by boiled tissues than by water alone, but we have not sufficient data to permit of speculation as to whether this indicates a thermostabile lipase, or an excess of hydrolysis by water in the presence of colloids.

The materials used were as follows:

Lipoma X.—Mixed material, obtained by removing fat from three subcutaneous lipomas from different persons.

Lipoma A.—Tissue from a single large subcutaneous lipoma.

14. Taylor: Jour. Biol. Chem., 1906, ii, 87.

Lipoma B.—Diffuse lipoma of the neck, "Madelung's Neck"—freed from fat.

Fibrosarcoma.—A large retroperitoneal tumor from a cow, extracted with ether.

Sarcoma of the Liver.—An alveolar sarcoma of the liver of a cow, not known whether primary or secondary. Ether extracted.

Omental Fat Tissue.—Normal tissue from a moderately emaciated tuberculous patient, freed from fat by ether.

Perirenal Fat.—From same subject, ether extracted.

Subcutaneous Fat.—From the same subject, ether extracted.

The results of the experiments are summarized in the accompanying tables 1, 2, 3 and 4.

TABLE 1.—TRIACETIN

Days Incubation	1	3	5	7	14	Total	Daily Aver.
Water only (2 c.c. ester)	0.10	0.39	0.51	0.62	0.74	2.36	0.17
Lipoma X, boiled (2 c.c. ester)	1.53	1.96	2.77	3.21	3.14	8.45	0.60
Lipoma X, fresh (2 c.c. ester)	4.29	6.60	6.65	6.80	7.19	31.43	2.24
Lipoma A, boiled (2 c.c. ester)	1.00	1.30	1.64	2.20	2.18	8.32	0.60
Lipoma A, fresh (2 c.c. ester)	3.40	5.20	7.12	8.13	8.46	32.31	2.30
Lipoma B, boiled (2 c.c. ester)	2.80	2.80	2.72	7.32	0.52
Lipoma B, fresh (2 c.c. ester)	12.81	17.38	17.48	47.67	3.40
Fibrosarcoma, boiled (2 c.c. ester)	1.91	2.41	2.35	6.67	0.47
Fibrosarcoma, fresh (2 c.c. ester)	10.42	13.40	12.60	36.42	2.60
Sarcoma of liver, boiled (2 c.c. ester)	2.08	1.94	2.01	6.03	0.43
Sarcoma of liver, fresh (2 c.c. ester)	13.11	19.08	20.00	52.19	3.73
Omental fat tissue, boiled (4 c.c. ester)	3.45	3.90	4.59	6.45	18.39	1.31
Omental fat tissue, fresh (4 c.c. ester)	8.45	12.42	15.01	23.35	59.23	4.23
Perirenal fat tissue, boiled (4 c.c. ester) ...	3.20	3.90	6.40	13.50	0.96
Perirenal fat tissue, fresh, (4 c.c. ester) ...	11.65	15.75	27.00	54.40	3.90
Subcutaneous fat tissue, boiled (2 c.c. ester) .	1.98	2.01	2.71	2.50	8.30	0.83
Subcutaneous fat tissue, fresh (2 c.c. ester) .	3.16	3.00	5.00	5.30	16.46	1.65

TABLE 2.—ETHYL BUTYRATE

Days Incubation	1	3	5	7	14	Total	Daily Aver.
Water only (4 c.c. ester)	0.14	0.19	0.10	0.27	0.31	1.01	0.07
Lipoma X, boiled (2 c.c. ester)	0.50	0.51	0.60	0.46	0.67	2.74	0.30
Lipoma X, fresh (2 c.c. ester)	2.23	3.04	3.01	2.27	4.86	15.41	1.10
Lipoma A, boiled (4 c.c. ester)	0.89	0.89	0.98	0.90	1.12	4.38	0.31
Lipoma A, fresh (4 c.c. ester)	3.66	5.11	6.81	5.00	7.42	28.00	2.00
Fibrosarcoma tissue, boiled (4 c.c. ester) ...	1.39	1.31	1.27	3.97	0.28
Fibrosarcoma, fresh (4 c.c. ester)	4.68	5.60	5.55	15.83	1.13
Sarcoma of liver, boiled (4 c.c. ester)	1.12	1.18	1.15	3.45	0.25
Sarcoma of liver, fresh (4 c.c. ester)	2.36	2.80	2.76	7.92	0.56
Omental tissue, boiled (4 c.c. ester)	1.33	1.78	2.10	1.95	7.16	0.51
Omental tissue, fresh (4 c.c. ester)	3.62	4.23	4.65	6.10	19.40	1.40
Perirenal fat tissue, boiled (4 c.c. ester)	1.55	1.43	1.87	4.85	0.35
Perirenal fat tissue, fresh (4 c.c. ester)	5.60	7.10	10.85	23.55	1.68

There being no significant difference between lipoma tissue and ordinary fatty areolar tissue in regard to their activity in hydrolyzing esters, it was thought well to see if the lipoma fat itself differed from

normal fat in the degree or ease with which it is hydrolyzed by tissue and pancreatic extracts. The following experiments do not indicate that lipoma fat is peculiar in respect to its hydrolysis by pancreatic lipase. Fat was obtained alike from lipomas and normal subcutaneous and omental fat tissues, by extracting the fresh tissues in the cold with ether and removing the ether at low temperature. In two experiments 5 c.c.

TABLE 3.—LIPOMA FAT

Days Incubation	1	3	5	7	14	Total	Daily Aver.
Water alone (2 c.c. fat)	0.07	0.08	0.17	0.15	0.20	0.67	0.05
Lipoma A, boiled (2 c.c. fat)	0.17	0.42	0.60	0.53	0.72	2.44	0.17
Lipoma A, fresh (2 c.c. fat)	0.27	0.46	0.64	0.42	0.68	2.47	0.17
Lipoma B, boiled (2 c.c. fat)	1.20	1.10	0.87	3.17	0.23
Lipoma B, fresh (2 c.c. fat)	1.53	1.45	1.06	4.04	0.29
Fibrosarcoma, boiled (2 c.c. fat)	0.57	0.51	0.42	1.50	0.11
Fibrosarcoma, fresh (2 c.c. fat)	0.51	0.58	0.40	1.49	0.11
Sarcoma of liver, boiled (2 c.c. fat)	0.37	0.12	0.32	0.81	0.06
Sarcoma of liver, fresh (2 c.c. fat)	1.23	1.20	0.65	3.08	0.22
Omental tissue, boiled (4 c.c. fat)	0.60	0.60	1.33	1.50	4.03	0.29
Omental tissue, fresh (4 c.c. fat)	1.50	1.22	1.76	1.74	6.22	0.44
Perirenal fat, boiled (4 c.c. fat)	0.83	1.0	1.42	2.25	0.16
Perirenal fat, fresh (4 c.c. fat)	0.82	2.0	1.89	5.71	0.41

TABLE 4.—OLIVE OIL

Days Incubation	1	3	5	7	14	Total	Daily Aver.
Water alone (2 c.c. oil)	0.06	0.0	0.1	0.0	0.1	0.26	0.02
Water alone (2 c.c. oil)	0.0	0.0	0.0	0.0	0.09	0.09	0.01
Boiled lipoma tissue X (2 c.c. oil)	0.05	0.03	0.14	0.13	0.20	0.55	0.04
Fresh lipoma tissue X (2 c.c. oil)	0.61	0.32	0.22	0.17	0.25	1.57	0.11
Boiled lipoma tissue A (2 c.c. oil)	0.0	0.0	0.0	0.14	0.10	0.24	0.02
Fresh lipoma tissue A (2 c.c. oil)	0.17	0.28	0.24	0.36	0.42	1.47	0.11
Boiled fibrosarcoma (2 c.c. oil)	0.30	0.13	0.05	0.48	0.03
Fresh fibrosarcoma (2 c.c. oil)	0.40	0.15	0.07	0.52	0.04
Sarcoma of liver, boiled (2 c.c. oil)	0.23	0.07	0.27	0.57	0.04
Sarcoma of liver, fresh (2 c.c. oil)	1.36	0.58	0.58	2.52	0.18
Omental tissue, boiled (4 c.c. oil)	0.0	0.0	*	*	?	?
Omental tissue, fresh (4 c.c. oil)	1.12	0.47	1.70	0.87	4.16	0.30
Perirenal fat, boiled (3 c.c. oil)	0.15	0.20	0.56	0.91	0.06
Perirenal fat, fresh (3 c.c. oil)	1.75	1.00	2.56	5.31	0.38

*Infected

lipoma fat and 5 c.c. normal fat were each acted on by 50 c.c. of a 10 per cent. emulsion of fresh dog pancreas. The mixture was first neutralized to phenolphthalein, then after six days in the incubator (with toluene) the watery emulsion was approximately neutralized with $n/10$ NaOH. After further incubation for two weeks in Experiment B, and three weeks in Experiment A, the emulsions were shaken out with equal volumes of

ether which had been neutralized to phenolphthalein, and the ethereal extracts washed by shaking out with water. The resulting ethereal extract was titrated with $n/10$ alcoholic NaOH, and the results were found to agree with each other as closely as could be expected with the materials and methods — as shown in Table 5.

TABLE 5.—COMPARISON OF THE HYDROLYSIS OF LIPOMA FAT AND NORMAL FAT

	Lipoma Fat	Normal Fat
A. Titration in H ₂ O sol., 5 days.....	87.5	90.8
B. Titration in H ₂ O sol., 5 days,	64.8	59.4
A. Titration in ether sol., 3 weeks	30.3	36.15
B. Titration in ether sol., 2 weeks.....	19.1	22.3

SUMMARY

The literature lacks satisfactory evidence to establish the generally accepted statement that simple subcutaneous lipomas do not give up their fat to the body during emaciation, although there are certain, more or less incomplete observations in support of this contention, and also definite cases which are entirely at variance with it; there is no question that it is correct for fatty sarcomas. All reported analyses indicate that the fats of lipomas are identical with the fats of normal fat deposits. A series of experiments has also failed to indicate any lack of ability on the part of lipoma tissue to hydrolyze various fats and esters which are also hydrolyzed by normal fatty areolar tissues. No reliable method could be devised which would indicate whether lipomas and normal fat tissues differ in their quantitative action on fats and esters. Lipoma fat is hydrolyzed by pancreatic lipase as readily as is normal human adipose tissue.

THE UTILIZATION OF PARENTERALLY INTRODUCED SERUM *

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PHILADELPHIA

The question as to how completely foreign proteins introduced parenterally can be utilized by the animal organism is one that has been under discussion and investigation for more than forty years. The earliest method of attack was that of injecting a protein, such as egg-white or foreign blood-serum and testing the urine for coagulable protein, on the assumption that if the protein could not be utilized by the body it would be eliminated promptly in the urine in coagulable form. If, therefore, no coagulable protein was found after such injection the protein was supposed to have been utilized by the body. Stokvis,¹ Ponfick,² Ott³ and Lilienfeld⁴ have reported experiments of this type and have found that in the dog and the rabbit the injection of egg albumin is followed by albuminuria while injection of blood-serum is not. Other proteins of animal or vegetable origin likewise varied in their power to produce albuminuria.

With the development of the precipitin reaction a new method of approaching this problem was at hand. Hamburger⁵ studied the results of the subcutaneous injection of egg-white into the rabbit and found that the serum of the rabbit ceased within about a day to show the presence of egg-albumin by the precipitin test. He also noted that on repeated injections of egg-white into the rabbit, it in time ceases to react by the

*From the John Herr Musser Department of Research Medicine, University of Pennsylvania; aided by a grant from the Committee on Scientific Investigation of the American Medical Association.

1. Stokvis, B. J.: Hühner Eiweiss u. Serumeiweiss u. ihr Verhalten z. thierisch. Organismus. *Zentralbl. f. d. med. Wissensch.*, 1864, ii, 596.

2. Ponfick: *Exper. Beiträge z. Lehre v. d. Transfusion. Arch. f. path. Anat. u. Phys. u. f. klin. Med.*, 1875, lxii, 273.

3. v. Ott: Ueber den Einfluss d. Kochsalzinfusion auf d. verbluteten Organismus im Vergleich m. anderen z. Transfusion verwendet. Flüssigkeiten. *Arch. f. path. Anat. u. Phys. u. f. klin. Med.*, 1883, xciii, 114.

4. Lilienfeld: *Ztschr. f. phys. u. diät. Therap.*, 1899. Quoted by Lommel, See Note 11.

5. Hamburger, F.: Zur Frage d. Immunisierung zg. Eiweiss. *Wien. klin. Wehnschr.*, 1902, xv, 1188; *Arteigenheit u. Assimilation*, Leipzig-Wien, 1903; Hamburger, F., and v. Reuss, A.: *Die Folgen parenteral Injektion v. verschieden genuinen Eiweisskörpern. Wien. klin. Wehnschr.*, 1904, xvii, 859.

development of albuminuria. Michaelis and Oppenheimer⁶ observed the same fact and noted that about the time the albuminuria ceases to follow the injection, the rabbit's serum contains a specific precipitin against egg-albumen. They advanced the hypothesis, therefore, that the precipitin is a denaturing agent which takes part in breaking down the foreign protein. This explanation cannot be applied to all animals, for Hamburger found that the dog is incapable of developing precipitins to foreign protein, as did also Friedenwald and Isaac.⁷ Hamburger and Moro⁸ have studied in man and the rabbit the time during which horse-serum could be demonstrated in the blood after subcutaneous injection. In three children they found, by the precipitin test, horse-serum (antitoxin) in the circulating blood for nineteen to thirty-one days after injection, and in each instance there developed in the child's serum, two to three days before the disappearance of the horse-protein from the blood, a specific precipitin against horse-serum. In the rabbit the horse-protein was demonstrable by the precipitin test for eight days, regardless of whether a large or a small injection had been given; and a specific precipitin against horse-serum developed in the rabbit's blood between the sixth and eighth days.

Later Hamburger and Sluka⁹ studied, both by the precipitin test and by determining the antitoxic activity, the persistence of tetanus antitoxin (horse-serum) in the dog, goat and cat, after subcutaneous injection. By both methods they found a persistence of the foreign protein in almost undiminished quantity for five to seven days, at which time, however, a sudden, rapid diminution in the quantity occurred. To explain this entire group of findings with the precipitin test, Hamburger has advanced the hypothesis that the horse-serum is distributed in the circulating blood, neither utilized nor excreted, until the body, after a latent period, develops the power of breaking up the foreign protein.

Friedenwald and Isaac,⁷ however, have found evidence that the substance essential to the precipitin reaction and stimulating the formation of a specific precipitin in the host is not identical with the whole protein injected and that the persistence of this essential substance cannot be taken as evidence of the persistence of the whole protein. They have injected horse-serum into both fasting dogs and dogs on a nitrogen

6. Michaelis, L., and Oppenheimer, C.: Ueber Immunität gegen Eiweisskörper, *Arch. f. Physiol. (Engelmann)*, 1902, Suppl., 336; Oppenheimer, C.: Ueber d. Schicksal d. mit Umgehung d. Darmkanals eingeführten Eiweissstoffe; Hofmeister's Beiträge z. chem. Phys. u. Path., 1904, iv, 263.

7. Friedenwald, U., and Isaac, S.: Weitere Untersuch. u. d. parenteral Eiweissstoffwechsel. *Ztschr. f. exper. Path. u. Therap.*, 1907, iv, 830.

8. Hamburger, F., and Moro, E.: Ueber d. biolog. nachweisbar Veränderung d. menschlich. Blut nach d. Seruminjektion. *Wien. klin. Wchnschr.*, 1903, xvi, 445.

9. Hamburger, F., and Sluka, E.: Ueber d. Verdaunungsfähigkeit d. Körperzellen, *Wien. klin. Wchnschr.*, 1905, xviii, 1323.

balance, and have studied the elimination of nitrogen in the urine, and also, by the use of the precipitin test and the complement deviation method, have studied the persistence of the foreign protein in the serum. Their chemical studies were made, with one exception, after subcutaneous injection; the biological studies, after intravenous injection. While their studies by the precipitin method confirm Hamburger's work, they find by the complement deviation method a gradual diminution of the foreign protein in the blood, beginning in the first twenty hours and continuing for eight to ten days. Moreover, in their studies of the urine, they observed almost always within the first forty-eight hours a quantitative elimination of the nitrogen injected. This result will be discussed later.

Studies based on the nitrogen elimination in the urine have been of two types: (1) those on fasting animals; (2) those on animals in nitrogen equilibrium. We will consider these separately.

EXPERIMENTS ON FASTING ANIMALS

Forster¹⁰ reports that after injecting both egg-white and horse-serum into fasting dogs an increased output of urea occurs. Lommel¹¹ in a series of investigations on seven fasting dogs recovered from 50 to 100 per cent. of the nitrogen (1.5 gm.) of swine-serum introduced intravenously, and most of this within six to twelve hours. Friedenwald and Isaac injected dog-, horse- and goat-serum and egg-albumen subcutaneously into dogs that had fasted from eleven to fourteen days. In all the experiments they found an increased output of nitrogen approximating the amount introduced. They quote also a personal communication from Loewy. He studied the nitrogen elimination of a fasting dog for three days before and three days after a transfusion of blood containing about 3 gm. of nitrogen (amount of blood determined by change in weight of donor) and noted after transfusion an increased elimination of 1.48 gm. In all these experiments there was a definite increase of nitrogen elimination following the nitrogen injection. An experiment of Michaelis and Rona¹² gave a different result. They studied a fasting dog for five days before and seven days after a subcutaneous injection of 100 c.c. of dog-serum, containing 1.15 gm. nitrogen, and obtained no increase in the output of nitrogen. The value of their results, as well as those of Friedenwald and Isaac, is greatly diminished by the fact that their injections were made subcutaneously instead of intravenously.

10. Forster: *Ztschr. f. Biol.*, 1875, xi, 496. Quoted by Friedenwald and Isaac, Note 7.

11. Lommel, F.: *Ueber d. Eiweissabbau b. parenteral Eiweisszufuhr.* *Arch. f. exper. Path. u. Pharm.*, 1907, lviii, 50.

12. Michaelis, L.: and Rona, P.: *Untersuch. über d. parenteral Eiweissstoffwechsel.* *Arch. f. d. ges. Physiol.*, 1908, cxxiii, 406.

EXPERIMENTS ON ANIMALS IN NITROGEN EQUILIBRIUM

Lommel brought four dogs into nitrogen equilibrium. Into three he introduced dog-serum intravenously; the fourth received blood by transfusion. In none of these experiments did he find an increase in the nitrogen elimination, but when heated serum was injected he obtained promptly a quantitative elimination of the nitrogen injected. Friedenwald and Isaac, on the other hand, placed a twelve-kilo dog on a daily diet of 120 gm. horse flesh and 50 gm. bacon. They then injected, subcutaneously, 160 c.c. of dog-serum containing 1.37 gm. nitrogen and during the following four days obtained an elimination of 1.51 gm. of nitrogen in excess of the nitrogen of the diet.

It will be seen that the results obtained by these investigators are far from uniform.

An experiment which is a combination of the feeding and fasting methods is the following: Carter¹³ fed a dog by mouth until it was in nitrogen equilibrium, and then ceased feeding by this method and gave for thirteen days hypodermic injections of peptonized skimmed milk and glucose. He concluded as the result of these observations that it is possible by this method to keep a dog, at least for a short time, in nitrogen equilibrium. His animal, however, received during the thirteen days of the injection period, quantities of glucose varying from 32 calories per kilo to 9 calories per kilo daily—always a quantity below the animal's caloric needs. Still more objectionable, however, is the fact that apparently more carbohydrates were given on those days on which more nitrogen was given and as undoubtedly an increase in the supply of carbohydrates tends to reduce the nitrogen catabolism the experiment is not entirely conclusive.

The irregularity in the results obtained by different observers both in fasting animals and those on nitrogen balance is, we think, explicable, and on the basis of our explanation we consider neither method suitable to the study of the question in hand. A fasting animal, when its stores of glycogen and of fat have been considerably reduced, will immediately deaminate introduced protein, utilize it to supply its caloric needs and excrete the nitrogen promptly as urea. Almost all the experiments reported in the literature on fasting animals are most readily thus explained. On the other hand, it is well known that an animal in nitrogen equilibrium eliminates promptly the greater part of any additional nitrogen administered, and thus Friedenwald and Isaac's experiments in the second group may be explained. If, however, an animal be given a nitrogen-free diet, containing sufficient carbohydrate and fat adequately to meet its caloric needs, its nitrogen excretion will be reduced

13. Carter, H. S.: Metabolism Experiments in Artificial Nutrition. *THE ARCHIVES INT. MED.*, 1908, i, 335.

to a minimum representing simply the end-product of the minimal tissue catabolism. If now there is administered a nitrogenous substance which can be completely utilized for replacing this tissue waste there will be no nitrogenous residue, the cellular catabolism will not be increased and the daily excretion of nitrogen will remain unchanged, still representing the daily cellular catabolism. If, however, a nitrogenous substance is administered which cannot be utilized for rebuilding tissues, the nitrogen thus administered will be excreted as well as the nitrogen of the daily cellular catabolism and the daily nitrogen elimination will be increased by the amount of nitrogen administered. This method has been used by Michaud¹⁴ for studying the extent of utilization of various proteins given by mouth and also more recently for other purposes by McCollum.¹⁵ In only one experiment in the literature, so far as we can determine, has the question of utilization of parenterally introduced protein been approached by this method. This is one of the experiments of Friedenwald and Isaac in which they placed a dog on a nitrogen poor (potato) diet and then injected egg-albumin. In this experiment only a slight increase in the nitrogen elimination followed the injection and this was referable to coagulable protein. These authors, however, have not used this method with other proteins and all their chemical studies were made after subcutaneous injections except in one experiment in which a fasting dog was given horse-serum intravenously. We therefore believed it to be worth while to again approach the problem from the chemical side, to place the animals on a suitable diet, use intravenous injections and, also, instead of giving only one injection of the protein to give injections daily for two or three successive days.

METHODS

Our procedure has been to place each dog on a diet of butter, rendered nitrogen-free by ether extraction, and of cane sugar in quantities sufficient to maintain a minimal nitrogen elimination without producing either diarrhea, glycosuria or vomiting. Usually this required from 70 to 85 calories per kilo. Each dog was fed daily at 5 p. m. The food was well borne and was eagerly eaten throughout the experimental periods reported. At 9 a. m. the dog was given a definite quantity of water and salt by stomach-tube and at 2 p. m. was catheterized and the twenty-four-hour urine taken. After a preliminary period of several days the nitrogen of the urine was estimated by the Kjeldahl method daily for three or four days. For the next two or three days, immediately after catheteri-

14. Michaud, L.: Beiträge zur Kenntnis d. physiolog. Eiweissminimum. *Ztschr. f. physiol. Chem.*, 1909, lix, 421.

15. McCollum, E. V.: Nature of the Repair Processes in Protein Metabolism, *Am. Jour. Physiol.*, 1911, xxix, 215.

zation, the animal was given intravenously each day an amount of blood-serum containing nitrogen approximately equal to that which the animal had been eliminating daily during the control period. In all other respects the régime, including the diet, was unchanged. Finally the same régime and diet and the nitrogen analyses were continued for a few days after cessation of the injections. In the early experiments the feces were collected as often as voided, which was only once in several days, and their nitrogen content estimated by the Kjeldahl method. As, however, the feces contained an amount of nitrogen equivalent to only 0.02 to 0.047 gm. daily, the analysis of the feces was omitted in the later experiments. The urine was examined daily for coagulable protein by the heat and acetic acid method and for glucose by the Fehling method, and for diacetic acid by ether extraction and the ferric chlorid test.

AUTHOR'S EXPERIMENTS

EXPERIMENT 1.—A female dog weighing 6,530 gm., was placed, on February 10, on a diet of 9 gm. nitrogen-free butter, 95 gm. cane sugar, 500 c.c. water and 1 gm. sodium chlorid daily. The injections of dog serum were made into a small vein of the leg under ether anesthesia. The results are shown in Table 1.

TABLE 1.—NITROGEN AND COAGULABLE PROTEIN ELIMINATION IN EXPERIMENT 1

24 Hours Beginning 2 p. m.	Weight in Grams	Serum Injected in c.c.	Nitrogen of Serum in Gms.	Volume of Urine in c.c.	Nitrogen of Urine in Gms.	Coagulable Protein
Feb. 14	6,640	110	.96	Very faint trace
Feb. 15	6,390	210	1.12	Very faint trace
Feb. 16	6,455	360	1.12	Very faint trace
Feb. 17	6,450	100	1.05	340	1.10	Very faint trace
Feb. 18	6,460	100	1.05	280	.88	Very faint trace
Feb. 19	6,240	100	1.05	230	.89	Very faint trace
Feb. 20	6,280	275	.85	Very faint trace
Feb. 21	6,300	290	.87	Trace

The table shows that no increase in the elimination of nitrogen during or following the period of serum injections occurred and that no significant quantity of coagulable protein appeared in the urine. Glucose and diacetic acid were not present. The conclusion is inevitable that the serum injected was completely utilized by the body for cellular anabolism.

It should perhaps be stated that the gradual fall in the nitrogen elimination is the characteristic fall that constantly occurs in an animal on a calorically adequate, nitrogen-free diet, and which, as noted by McCollum,¹⁵ continues to the seventeenth day.

This experiment was performed with practically the same results on another dog except that during the first day of the injection period the food was vomited, owing to the animal having been fed too soon after etherization.

EXPERIMENT 2.—A female dog weighing 6,230 gm. was placed, on January 24, on a diet of 8.7 gm. nitrogen-free butter, 98 gm. cane sugar, 500 c.c. water and 1 gm. sodium chlorid daily. The injection of dog-serum was made into a small vein of the leg under ether anesthesia. The results are shown in Table 2.

TABLE 2.—SHOWING EXCRETION OF NITROGEN AND COAGULABLE PROTEIN IN EXPERIMENT 2

24 Hours Beginning 2 p. m.	Weight in Grams	Serum injected in c.c.	Nitro- gen of Serum in Gms.	Volume of Urine in c.c.	Nitro- gen of Urine in Gms.	Coagulable Protein
Jan. 28	6,070	520	1.25	None
Jan. 29	6,135	560	1.12	None
Jan. 30	6,090	380	1.01	None
Jan. 31	6,090	100	1.05	550	1.48	Vomited
Feb. 1	6,020	80	.84	425	1.14	Faint trace albumin
Feb. 2	6,020	80	.84	520	1.21	Faint trace albumin
Feb. 3	5,880	80	.84	340	1.07	Faint trace albumin
Feb. 4	5,955	330	0.98	Faint trace albumin
Feb. 5	5,890	410	0.99	Faint trace albumin

The urine was free from glucose and diacetic acid. On January 29 a control anesthetization was done quite similar to that used during the injections. Omitting the analysis on January 31, which is rendered worthless by the vomiting, we find the average elimination for five days, the three days before commencing, and the two days after ceasing injection, to be 1.08, the average elimination during the three days of injection 1.14. Here again we may conclude that practically all the nitrogen of the serum was utilized.

The same type of experiment was next tried with horse-serum instead of dog-serum. The horse-serum was obtained fresh and without preservative.

EXPERIMENT 3.—A female dog, weighing 6,375 gm. was placed, on January 22, on a diet of nitrogen-free butter and cane sugar the quantities being gradually increased until January 31 when the diet was fixed at 10 gm. butter, 113 gm. sugar, 300 c.c. water and 1 gm. sodium chlorid daily. The horse serum was injected into a small vein of the leg under ether anesthesia. The results were as shown in Table 3.

TABLE 3.—SHOWING EXCRETION OF NITROGEN OF URINE AND COAGULABLE PROTEIN IN EXPERIMENT 3

24 hours Beginning 2 p. m.	Weight in Grams	Serum injected in c.c.	Nitro- gen of Serum in Gms.	Volume of Urine in c.c.	Nitro- gen of Urine in Gms.	Coagulable Protein
Feb. 1	5,880	350	1.10	None
Feb. 2	5,878	470	1.28	None
Feb. 3	5,815	275	1.06	None
Feb. 4	5,850	80	.74	430	1.23	None
Feb. 5	5,750	80	.74	450	1.35	None
Feb. 6	5,810	80	.74	290	1.23	None
Feb. 7	5,780	180	1.10	Trace

Traces of glucose and diacetic acid were found on February 7, and as appetite failed at this point the experiment was brought to an end. In this experiment the average elimination of the three control days of the fore period and the one day of after period was 1.13; of the three days of injections, 1.27. Here also it is evident that the serum has been completely or almost completely utilized. A second similar experiment, owing to the larger amount of serum injected, gave even more conclusive results.

EXPERIMENT 4.—A female dog, weighing 7,070 gm., was placed on a diet of nitrogen-free butter and cane sugar, on March 2. From March 14 to 16 it received daily 8 gm. of nitrogen-free butter, 100 gm. cane sugar, 500 c.c. water, and 1 gm. sodium chlorid; from March 17 to 21 the butter was reduced to 6.5 gm. daily. The horse-serum was injected into a small vein of the leg, under ether anesthesia.

TABLE 4.—URINE NITROGEN AND COAGULABLE PROTEIN EXCRETION IN EXPERIMENT 4

24 Hours Beginning 2 p. m.	Weight in Grams	Serum injected in c.c.	Nitro- gen of Serum in Gms.	Volume of Urine in c.c.	Nitro- gen of Urine in Gms.	Coagulable Protein
March 15	6,330	425	1.33	Very faint trace
March 16	6,360	155	1.36	Very faint trace
March 17	?	500	1.37	Very faint trace
March 18	6,275	120	1.60	480	1.52	Very faint trace
March 19	6,180	100	1.32	447	1.19	Very faint trace
March 20	6,120	305	1.11	Very faint trace
March 21	6,110	333	1.11	Very faint trace

No glucose or diacetic acid appeared in the urine. Here again is presented definite evidence of complete or almost complete utilization of the foreign serum. Whether the slight rise noted in both Experiments 3 and 4 is a coincidence or is due to a small fraction of the serum that is not utilized and is therefore eliminated, or is due to a toxic action of the serum, causing a slight increase in catabolism, it has been impossible to determine. Toxic action, however, is rendered improbable by the fact that no increase in temperature was noted during the period of serum injection.

We believe that these experiments demonstrate, so far as can be shown by the chemical method, that the dog is able to utilize completely, homologous serum, parenterally introduced and completely, or almost completely, horse-serum similarly introduced. We differ, therefore, from Friedenwald and Isaac, who concluded that the dog cannot utilize parenterally introduced horse-serum. We believe that their conclusions, based on their chemical studies, are incorrect owing to the method they employed; that is, the use of dogs either fasting or on a nitrogen balance. It is also worthy of note that the marked toxic effects which they noted in dogs receiving injections of horse-serum after being fed on a flesh diet

(usually horse flesh) were absent in our experiments with a butter and sugar diet. Also their observations on the persistence of horse-serum protein injected intravenously into the dogs, as measured by the complement deviation test, is of much interest in connection with our chemical studies. The gradual diminution, beginning soon after injection and continuing for several days, which they demonstrated in the amount of the complement deviating substance persisting in the circulation of the injected dog, is precisely the gradual diminution that one must expect if, as we believe, the horse-serum protein distributes itself evenly throughout the blood of the injected dog and is gradually utilized by the dog, simultaneously with the dog's own blood protein, at a rate proportional to the foreign protein's concentration in the dog's blood. We believe, therefore, that the complement deviation experiments of Friedenwald and Isaac with our own chemical studies afford strong evidence that the dog can utilize both homologous serum and horse-serum, introduced intravenously, as a source of tissue nitrogen.

CONCLUSIONS

1. In order to use changes in the elimination of nitrogen as a basis for deductions concerning the utilization of nitrogenous substances parenterally introduced, the animal must be on a calorically adequate, nitrogen-free diet.

2. A dog on such a diet and receiving intravenously an amount of nitrogen, in the form of dog-serum, approximately equal to that being eliminated, shows no increased elimination of nitrogen.

3. When a foreign serum, as horse-serum, is injected instead of dog-serum, the nitrogen elimination is increased very little, if at all.

4. The dog, therefore, is able to utilize completely for anabolic processes the protein of dog-serum and all, or almost all, of the protein of horse-serum introduced intravenously.

"LOW FEVER" *

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For a number of years, but during the past summer particularly, our attention has been directed to a clinical picture variously known as "continued fever," "sun fever," "Wilmington fever," "low fever," etc., the only constant symptom of which is a supposedly continuous elevation of temperature. That this supposition is incorrect can be easily determined by taking the temperature throughout the twenty-four hours, when it will be found that during the night the "fever" disappears. But as these patients do not feel ill, and do not go to bed, they are seen by the physician only during the day; hence the idea of a continuous elevation of temperature. As very little has appeared in the literature concerning this condition, a fuller description of this so-called "low fever" seems desirable, more especially for the sake of differential diagnosis.

The causes of continued fever in the northern part of the temperate zone, as laid down by Cabot¹ for New England, are typhoid fever, tuberculosis and sepsis. In the southern states there must be added as causes of continued fever the malarial fevers,² Malta fever,³ hepatic abscess of amebic origin,⁴ and in the tropics trypanosomiasis and kala azar.

In this locality the chief difficulty lies in differentiating tuberculosis, for during the past decade a mass of accurate statistics on the prognosis of tuberculosis has become available, showing that the earlier the diagnosis is made and the sooner treatment is commenced, the better are the chances for arrest or recovery. This showing has naturally increased the desire for the earliest possible diagnosis.

The various tuberculin reactions and the Roentgen ray have taught us that periods of malaise with a rise of a degree in temperature, are frequently the manifestations of a slight or of an early tuberculous infection, even in the absence of physical signs in the chest and of clinical pulmonary symptoms.

In this particular locality the tropical fevers, including astivo-autumnal malarial fever,⁵ are unknown, so that after excluding amebic

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1. Cabot, R. C.: *The Three Long Continued Fevers of New England*. Boston Med. and Surg. Jour., Aug. 29, 1907; *Differential Diagnosis*, p. 389.

2. Craig, C. F.: *The Malarial Fevers*, 1909, Wm. Wood & Co.

3. Ferenbaugh, T. L.: *Endemic Mediterranean Fever (Malta Fever) in Southwest Texas*, Jour. Am. Med. Assn., 1911, xlvii, 730.

4. Rogers, L.: *Fevers in the Tropics*, ed. 2, p. 379.

5. Allan, W.: *Charlotte Med. Jour.*, 1911, lxiv, 165.

hepatitis and amebic abscess of the liver, malaise with a slight daily rise of temperature without leukocytosis should be considered presumptive evidence of a tuberculous infection. But we submit that an early diagnosis cannot be made by exclusion in this latitude, and that the cases so diagnosed are subjected to unnecessary mental anguish and their condition is thereby aggravated, because of such a diagnosis.

In the tropics this "low fever" was some years ago singled out from among the unclassified non-specific continued fevers.

HISTORICAL

In 1894 A. Crombie⁶ (a) gave a very good description of this condition as follows:

It is one which is only occasionally met with among Europeans, and I do not think I have met with it in the natives in India, but if it does occur among them it would hardly be brought under my notice. I refer to a persistent low elevation of temperature unaccompanied by any constant symptoms of definite duration, and uninfluenced either by quinin or arsenic. The temperature never falls below 99 degrees and rarely rises above 101.5. It may continue for several weeks without complication except, perhaps, a tendency to diarrhea of a bilious character, with loss of appetite, and gradual loss of strength and flesh. Some of these cases are distinctly aggravated by quinin, and I have known them cease abruptly on withdrawing the drug which had been persistently given in the belief that the condition was malarial in its essential nature. These cases are spoken of as "low fever" and are generally cured by a "change" of any kind, but especially by a trip to sea, and it is especially this form of fever, which in Calcutta is benefited by a visit to the sandheads. Though very ill-defined, these cases constitute a distinct type of fever at once recognized when met with.

At the same time Ronald Ross,⁷ giving a classification of fevers for India, under the heading of simple or continued fevers, gives a subhead to "fever without any concurrent symptoms."

Again, in 1898, in his classification of "non-specific fevers of doubtful causation, probably climatic," Crombie⁶ (b) gives four classes, the last of which is "low fever."

In speaking of the effect of exercise on temperature he says:

And the gradation of symptoms from the mere temporary elevation of temperature which invariably accompanies exercise in the hot moist climate of Bengal (I have known my own temperature rise to 99.9 F. as the result of an hour's walk in the month of August) though a few hour's febricula or a few days of continued fever, up to ardent fever and siriasis, point rather to their being the result of a temporary paresis of the heat regulators under the embarrassments of the conditions of high temperature and humidity.

6. Crombie, A.: (a) Presidential Address on the Fevers of India. *Tr. First Indian Med. Cong.*, 1894, p. 17; (b) *The Unclassified Fevers of Hot Climates. Brit. Med. Jour.*, 1898, ii, 682; *Jour. Trop. Med.*, p. 128.

7. Ross, R.: *Tr. First Indian Med. Cong.*, 1894, p. 382.

In describing this low fever he says:

Low fever is of a distinctly different type from the foregoing climatic fevers (Nasha fever, etc.). It is characterized by a persistent low elevation of temperature of indefinite duration, without any specific symptoms, except those traceable to the feverish condition itself. It begins insidiously with slight malaise and anorexia. The temperature ranges from 99 F. in the morning to 101.5 F. in the evening, never falling below 99 F. and rarely rising above 101 F., and it may continue for many weeks, unaffected by quinin or arsenic, pushed to extreme doses, or by any other medicinal treatment, but usually yielding at once to change of climate. It would appear also to be due to embarrassment of the heat centers, because it ceases generally at once when the climatic conditions are improved by the patient going to the hills or to the sea. If it were due to a specific cause this would not be the case. If it were due to a microorganism in the blood, the cessation of the symptoms would not be as immediate as happens so constantly with this form of fever on change of climatic surroundings.

Manson⁸ gives practically the same account of "low fever" as Crombie, and speaks of it as "not an unusual one among Europeans in the tropics."

Rogers⁹ description of "low fever" is probably the best in the literature. He has encountered it in Europeans in the hot damp provinces of Bengal, Assam and Madras. His clinical description includes malaise, anorexia and nervous depression, with a rise of temperature during the daily activities to 99 F. or 100 F., or rarely to 101 F., with a return to normal during the early morning. The fever may continue through the next cold season, though, with Crombie, he finds that a change to a higher, dryer or colder climate causes immediate abatement of the temperature. Physical examination is negative, although he makes the surprising statement that "in very long cases some enlargement of the spleen may ultimately develop." He finds generally a leukopenia with a relative increase in the small mononuclear leukocytes to about 40 per cent. and a decrease of the polymorphonuclears to about 50 per cent., but with no marked increase in the large mononuclears. Rogers also suggests "an enfeeblement of the heat-regulating mechanism by prolonged strain as the essential cause of the excessive diurnal variation of the body temperature which occurs." He suggests the possibility of a leukocytozoan parasite, and cites the experience of Musgrave, Wherry and Woolley¹⁰ in Manila. His reference to Castellani's¹¹ four cases was probably not intended to refer to this class of fever, as all of these cases were clearly infectious, and only one bore any near resemblance to "low fever" clinically; in this case there was severe diarrhea, and a bacillus was isolated from the feces which was agglutinated by the patient's blood.

8. Manson, Sir P.: *Tropical Diseases*, ed. 4, p. 320.

9. Rogers, L.: *Fever in the Tropics*, ed. 2, 1908, p. 193.

10. Musgrave, W. E., Wherry, W. B., and Woolley, P. G.: *Tropical Splenomegaly*. Bull. Johns Hopkins Hosp., 1906, xviii, 28.

11. Castellani, A.: *Notes on Cases of Fever Frequently Confounded with Typhoid and Malaria in the Tropics*. Jour. Hyg., 1907, vii, 1.

The description of "low fever" by Chalmers and Castellani¹² seems to apply to this infectious fever of low virulence, rather than to the clinical picture as first described by Crombie.

In our own cases we have encountered this low fever in persons who were overworked and underfed. Our series comprises three men and six women. It seems to be confined to the most active period of life, between the ages of 15 and 40 years. Our observations on negroes are too incomplete to compare its race incidence. Social condition and occupation seem to be without effect. Overstrain, mental or physical, is the predisposing cause. These cases all show loss of weight, a secondary anemia of varying degree and poor muscular tone. Their time is spent mostly indoors, and practically no exercise is taken. The caloric value of their diet is always considerably below normal, running from 20 to 28 calories per kilo of body-weight. The usual fatigue symptoms are in evidence, anorexia, nausea, flatulence, constipation or the early morning diarrhea which is liable to accompany any condition in which there is low blood-pressure (as pellagra, sprue, etc.), headache, vertigo, insomnia, early mental and muscular fatigue, backache and aching in the legs and knees.

The physical examination has been uniformly negative. There is no cough, sputum or night sweats, and all cases showing a positive von Pirquet tuberculin reaction have been excluded. The throats were gone over carefully, and all cases in which pus could be squeezed from the tonsils have been excluded from this series. We have found blood-pressure ranging from 90 to 115 mm. Hg. In some cases the pulse-rate has been increased. Hemoglobin estimations ran from 65 to 90 (Talqvist). In only a few instances were we able to confirm Rogers' findings of leukopenia with relative increase in the small mononuclear leukocytes and decrease in the polymorphonuclears. *Plasmodium vivax* (the only form of malarial organism occurring in Charlotte) was never present.

The fever curve itself was the only thing characteristic of the condition. Contrary to Crombie's statement, we find with Rogers, that the temperature returns to normal during the night; but contrary to Rogers' statement that the elevation of temperature makes its appearance in the middle of the day or early afternoon, we find it frequently appears during the first hour after rising in the morning, or following the first meal of the day; and, furthermore, that the temperature may fall below 99 F. and rise again at any time during the day. Usually the daily temperature has varied between 99 F. and 100 F., but at times reaching 100.6 F. This "low fever" generally appears about June, after a month's hot weather, and continues until the cooler weather of October, or until a vacation is taken. In cases that have recently become "run down" it may appear

12. Castellani and Chalmers: Manual of Tropical Diseases, p. 789.

TABLE GIVING ANALYSIS OF

Case	1	2	3	4
Color	M. S.	A. C.	E. E.	W. A. R.
Sex	White	White	White	White
Age	Male	Female	Female	Male
Age	30	24	21	38
Social Condition	S.	S.	S.	M.
Occupation	Druggist	Stenographer	Teacher	Businessman
Predisposing Causes	Steady overstrain	Nursing	Steady overstrain	Influenza 1 mo. ago
Duration of Fever	4 mo. in 1910	2 mo. in 1910	5 mo. in 1911	2 mo. in 1911
Recurrences	None	1908 1909 1910 1911 1912
Hours of Sleep	8.5	8	8	8
Hours of Work	13	9	7	8
Amount of Exercise	Standing all day	1 mile walk	None	1 mile walk
Diet	26 calories per kilo	24 calories per kilo
Weight	11 lbs. off in 4 mo.	18 lbs. off for 4 yrs.	6 lbs. off	Normal
Headache	None	Every 10 days	None	None
Insomnia	None	None	None	None
Tongue	Coated	Coated	Normal	Coated
Stomach	Sour	Sour	Attacks of pain when nervous	Nausea at times
Appetite	Poor	Poor		
Intestines	Constipation, Gas	Constipation, Gas	Takes daily purge
Pulse-rate	80	80	85
Blood-pressure	100	124
Muscular Tone	Worn out, aching by night	Very poor	Can hardly drag home	Fair; tired
Backache	Present	Present	Absent	Absent
Cough	None	None	None	None
Sputum	None	None	None	None
Night-sweats	None	None	None	None
Tuberculin Reactions	Negative to von Pirquet	Negative to von Pirquet	Negative to von Pirquet Koch	Negative to von Pirquet
White count	6,700	6,000	8,200
Differential
Polynuclear	64%	80%	71%
Small monos	24	15	18
Large monos	8	5	8
Eosinophils	5.4%	4	0	3
Hemoglobin	78%	80%	90%	80%
Red Count	4,320,000	4,470,000	5,000,000	4,000,000
Color Index	.89	.89	.90	1.00
Plasmodia	Negative	Negative	Negative	Negative
Feces	Normal	Normal	Normal
Urine	Conc.	Normal	Normal	Normal
Complications	None	Visceroptosis	None	None

AUTHOR'S CASES OF "LOW FEVER"

5	6	7	8	9
E. B. D. White Female 38 W.	E. White Female 21 S.	J. C. T. White Female 30 M.	J. E. S. White Male 40 M.	G. White Female 34 W.
Stenographer Steady over strain 3 mo. in 1911	School-girl Typhoid 3 months ago 1 mo. in 1911	Housewife 5 pregnancies in 7 years 1 mo. in 1911	Manufacturer Worry 4 mo. in 1911	Nurse Worry 6 mo. in 1911
1912
9 9	8 7	8 15	8.5 6	8.5 9
1 mile walk	None	Standing all day	None	Standing all day
28 calories per kilo 7 lbs. off 18 lbs. off in 9 mo. 24 lbs. off	20 calories per kilo 20 lbs. off	21 calories per kilo 31 lbs. off
Frontal (often)	Frontal a week at a time	Frontal	None (has vertigo)	Frequent for 3 years
Severe	At times	None	None Came on as wt. decreased
Normal Anorexia	Normal Normal	Normal Acid, Gnawing	Coated Anorexia	Normal Frequent Nausea
Bilious, con- stipated, gas	Normal	Takes daily purge	Diarrhea (early morn- ing) gas	Constipated 4 years
82 to 106 Low	90	60 to 70	80 to 100 90 95
Feels weak	General weakness	Tired in half a day	Poor	Poor
Present None None None	Present None None None	Present Negative None None	Absent None None None	Present None None None
Negative to von Pirquet	Negative to von Pirquet	Negative to von Pirquet	Negative to von Pirquet
.....	9,200	8,000	7,000	5,000
.....	Normal
.....	64%	70%
.....	25	24
.....	6	6
.8%	5	0
80%	85%	65%	90%	85%
.....	3,880,000	4,500,000	4,500,000
.....83	1.00	.94
Negative	Negative	Negative	Negative	Negative
.....	Normal	Normal	Normal	Normal
.....	Alkaline	Indican	Normal	Very Acid
Retroflexion	None	None	None	None

later in the summer, and in chronic cases it may continue interruptedly throughout the winter. In some of our cases it has recurred with great regularity every summer for a number of years.

A vacation to the coast or mountains may put an end to the "fever" at once, but this is particularly true of a change to the higher mountain resorts of the state, such as Blowing Rock (elevation 4,000 feet), where the nights are cold. For the sake of brevity we have tabulated our cases.

We believe that this "low fever" is simply an abnormal diurnal variation of the body temperature, due to a temporary instability of the heat-regulating mechanism, as stated by Crombie and by Rogers; this depression of the heat-regulating function being merely one expression of a general functional depression or state of chronic fatigue, dependent on under-nutrition and over-strain, and emphasized especially during the summer of 1911 by the unusual heat.

We shall proceed to discuss this proposition:

Butler¹³ gives the range of normal temperature as from 97.2 F. to 99.5 F., the average being 98.6 F. Both Butler and Howell¹⁴ state that muscular exercise may raise the temperature, Howell stating that if this initial rise of temperature occurs, it is a sign of imperfect heat regulation; that is, the extra amount of heat thus produced is not promptly gotten rid of. Both state that meals may raise the temperature, Butler giving as much as 0.4 F. Wunderlick's figures as given by Adami¹⁵ are sub-febrile to 100 F., low febrile to 100 F. to 101 F., moderately febrile 101 F. to 103 F., etc.

Heat production depends on the intake of food and on muscular exercise; heat loss depends on excretions (2 per cent.), on expired air (3.5 per cent.) and evaporation of water from the lungs (7 per cent.), on the evaporation of sweat (14 per cent.), and on radiation and conduction from the body surface (73 per cent.). Heat regulation is controlled mainly by sweating and radiation. "The control through the vasomotor nerves is doubtless even more important" (Howell); that is, dilatation of the skin capillaries means loss of heat; cold air contracts the skin capillaries and conserves heat. Howell says that neither heat centers nor heat nerves have been demonstrated, and further that,

Most physiologists perhaps believe that variations in heat production occur, as stated above, by alterations in the intensity of oxidations in the muscles, brought about by reflex excitation through the motor nerve fibers and that a special set of heat fibers does not exist. The unconscious regulation of the body temperature is effected chiefly through the following centers:

Heat Dissipation: 1. Sweat centers and sweat nerves. 2. Vasoconstrictor center and vasoconstrictor nerves. 3. Respiratory center.

Heat Production: 1. Motor nerve centers and motor nerve fibers to skeletal muscles. 2. Quantity and character of food as determined by the appetite.

13. Butler: *The Diagnostics of Internal Medicine*, ed. 2, 1906, p. 107.

14. Howell: *Text Book of Physiology*, 1906, p. 828.

15. Adami: *Principles of Pathology*, ed. 2, i, p. 481.

On the other hand, Adami¹⁵ says:

We must with MacAlister, predicate the existence of some central heat-controlling center regulating the (various) heat-producing and heat-discharging apparatus; a center which stimulates the former and inhibits the latter in order to raise the body temperature, and does the reverse in order to lower it. . . . All that is sure is that within the brain and spinal cord are nerve cells, which on stimulation lead, some of them, to increased production of heat by the tissues, others to increased loss of heat by the body surfaces. The wonderful regulation of the bodily temperature under ordinary conditions is a strong indication that controlling the production and the loss is one pair or an intimately connected system of heat-regulating centers.

As applied to our cases it seems obvious that their increase in temperature cannot be due to extra heat production by muscular activity, or increased food intake, as both of these functions are diminished; there must be, then, imperfect heat elimination. This diminished heat dissipation is not due to slower respiration, nor to vasoconstriction (there is vasodilation); it must be due then to either diminished radiation and conduction, or to imperfect evaporation from the skin, or to both. That diminished radiation and conduction play a considerable part in this condition is shown by the fact that these temperatures were recorded during the hot weather, and in the daylight, and that they returned to normal with the advent of cold weather. But diminished radiation and conduction alone is not a sufficient explanation, for, although the temperature rises when the daily activities commence, there is a definite limit in each case beyond which this rise will not go. What then fixes this limit and keeps the temperature below it? It must be the effect of the body heat on the sweat nerves, causing reflexly an increased sweating, with consequent loss of heat. H. Aron¹⁶ has demonstrated that animals exposed to the tropical sun soon die unless increased evaporation of water counteracts the increased heat absorption. He says, "Monkeys exposed to the sun in Manila die in a little over one hour because of their limited capacity to evaporate water, while man with his well-developed sweat glands resists the same climatic conditions for a much longer period without detriment"; and again, "The more perfect this water evaporation is, the better the normal body temperature may be maintained." In noting the inferiority of the white man to the black in effective sweating, he says, "It is as yet undecided whether the result is due to the color, or if the nervous regulation of the sweat glands, etc. . . ." He evidently considers the evaporation of sweat to be the method of heat regulation, as after exercise, even in temperate climates.

In comparing the action of the tropical sun on the skin temperature of Filipinos and Americans, he says:

16. Aron, H.: *Philippine Jour. Sc.*, Section B., 1911, vi, 126.

With the white skin this process (evaporation) takes place more slowly and it must be for this reason that the brown skin, while absorbing more heat, is found to have lower temperatures than the white skin under similar conditions. The regulatory apparatus of the brown is more sensitive and works more promptly and successfully.

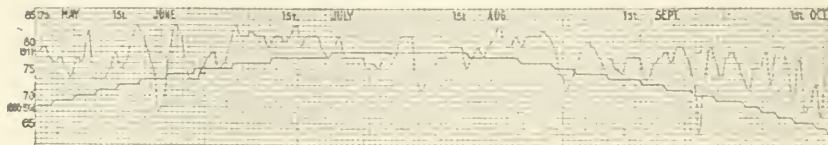


Chart 1.—Effect of the unusual heat of the summer of 1911 in producing "low fever."

In these fatigue cases, with general lowering of the functions, during normal activity in the season when radiation and conduction are lessened, the body temperature is regulated at from 99 to 100.4 during the day time. This phenomenon seems to be due to the lack of sensitiveness of the sweating are to a moderate increase in the body temperature in these individuals, and during ordinary activity the threshold of stimulation of the sweating are seems to be raised from 0.5 F. to 2 F.

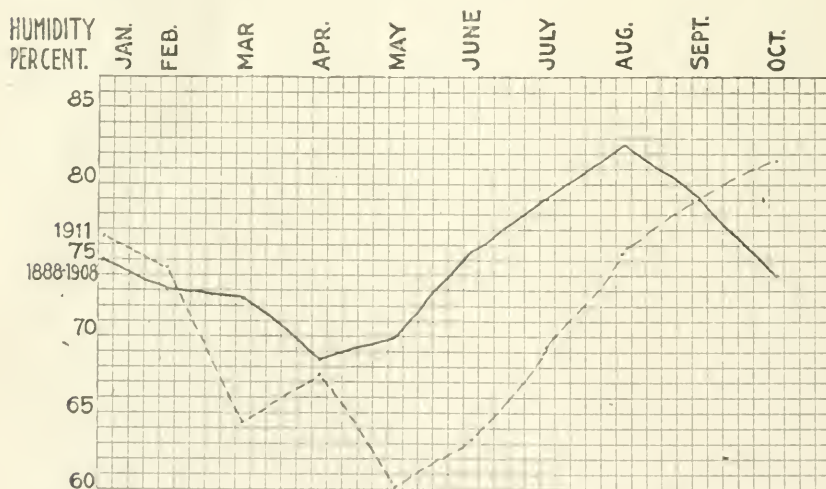


Chart 2.—A chart showing the average of morning and evening humidity in 1911 compared with the twenty years, 1888-1908, by months. (These data were obtained from the weather bureau office, Charlotte, through the kindness of Mr. Atto, Chief Observer.)

That this depression of the heat-regulating function is merely one expression of a general functional depression is easily apparent from the case series. That undernutrition and overstrain were present is also apparent from the accompanying chart, and in the absence of any other

demonstrable etiologic factors, these must be considered as the two chief causes of this condition. The part played by the unusual heat of the summer of 1911 can best be shown by Chart 1.

From May 1 to Nov. 1, 1911, 184 days, there were 131 days above the average temperature, thirteen days of average temperature, and forty days below the average temperature; from May 10 to October 23, 166 days, there were 128 above, ten equal to, and twenty-eight below the average temperature.

The severity of this heat was considerably modified by the low humidity, as shown in Chart 2.

The marked benefits to be derived from a change of scene are due to a relief from overstrain, and in many instances this is the only treatment needed to stop the "fever." In the more stubborn cases an improvement in nutrition is necessary before the temperature falls to its usual level, as is shown during the winter, when these patients regain their appetites and put on a little flesh.

The advantage of removal to high mountain sections over the Piedmont or tide-water regions, we believe, is entirely due to the cold, which restores appetite and promptly raises blood-pressure.

In conclusion then, we would point out that in the south we have a low fever, occurring during the summer months, which is only apparently continuous, and which is purely functional.

AN EXPERIMENTAL INVESTIGATION OF THE VALUE OF HEXAMETHYLENAMIN AND ALLIED COMPOUNDS *

CURTIS F. BURNAM, M.D.

BALTIMORE

This study was undertaken to determine the capacity of infected kidneys to excrete hexamethylenamin. We had just had a small series of unilateral kidney infections in which large doses of hexamethylenamin had failed to be of any benefit. The frequent clinical failure of the drug it was felt might depend on its inability to pass through such impaired organs. At the outset, full credence was placed in the generally current valuation set on hexamethylenamin, i. e., when taken by mouth, it is excreted in the urine, bile, pancreatic, synovial and cerebrospinal fluids in sufficient quantities to be of marked bactericidal value. This confidence, however, was not strengthened by a rather thorough review of its extensive literature, and personal experimental results which quickly developed gave still greater uncertainty. Ever since Nicolaier introduced it into medicine, nearly twenty years ago, the efficiency of the drug has been ascribed to its decomposition into formaldehyd. The authors, however, are quite vague, using such adjectives as, a little, partial and almost complete, in describing the extent of this decomposition, and not a few hold that hexamethylenamin is antiseptic itself independent of the formation of formaldehyd.

Nowhere has there been serious endeavor to ascertain how much hexamethylenamin or formaldehyd are present in the fluids of the body after giving the drug by mouth. Its accredited efficiency in the body fluids where it has been described, rests, first, on a demonstration of the existence of either hexamethylenamin or formaldehyd in the fluid; second, on clinical improvement, and third, on the reduction in the number of bacteria as shown by the plate-culture methods after its use. In my personal studies, the seemingly necessary steps were, first, a quantitative determination of the amount of hexamethylenamin excreted in the urine after giving known quantities by mouth; second, a quantitative estimation of the amount of free formaldehyd present; third, determination of the bactericidal power of hexamethylenamin; fourth, determination of the bactericidal power of formaldehyd; fifth, determination of the strongest solutions of hexamethylenamin and of formaldehyd which can be tolerated by the kidneys and other urinary organs; sixth, a comparison of the chemical and clinical findings.

*Manuscript submitted for publication in ARCHIVES July 11, 1912.

The third, fourth and fifth steps proved simple and yielded positive results, the details of which follow. Great difficulty, however, was met at the very outset in connection with securing suitable chemical methods for estimating the amounts of the substances in the fluids. Not only were the quantitative methods uncertain, but the qualitative procedures were equally unsatisfactory, principally because they reacted identically with hexamethylenamin and formaldehyd.

The most delicate qualitative test in use and one which has been extensively employed is that of Hehner. It consists in adding 5 or 6 drops of milk to a few c.c. of the fluid to be tested. This mixture is then stratified over a reagent made by adding one drop of a 3 per cent. ferric chlorid solution to 100 c.c. of 99 per cent. sulphuric acid. The presence of formaldehyd or hexamethylenamin is indicated by the slow formation at the line of juncture of a deep amethyst ring. The color of urine and bile seriously interfere with the test and require a preliminary distillation, which is accomplished by adding a little sulphuric acid and water, when formaldehyd gas passes off in the distillate.

The objections to this test are two-fold. First, that it does not differentiate between formaldehyd and hexamethylenamin, and second, because of its extraordinary delicacy. Formaldehyd clearly shows in solutions of 1 to 1,000,000 and hexamethylenamin in solutions of 1 to 500,000 or less. This is in the proportion of 1 c.c. of formaldehyd to 1,000 liters of water. By the thickness of the ring or the rapidity of its appearance I was completely unable to distinguish between solutions of 1 to 100,000 and 1 to 10,000, nor could I determine from the ring formation whether formaldehyd or hexamethylenamin was the substance present.

Through the valuable assistance of Dr. H. A. B. Dunning, I was fortunate in securing a very delicate test, and one which reacts to free formaldehyd, but not to hexamethylenamin. This test consists in adding to the suspected fluid, 3 drops of .5 per cent. aqueous solution of phenylhydrazin hydrochlorid and then 3 drops of a 5 per cent. aqueous solution of sodium nitroprussid; then an excess of saturated aqueous solution of sodium hydroxid. It is important that the solution to be tested as well as the sodium hydroxid be slightly warmed to a little more than body temperature. When formaldehyd is present in solutions of 1 to 20,000, or stronger, there follows an intense blue color which gradually changes to green and then after a few minutes to brown. In solutions of less than 1 to 20,000 the first color is the intense green which passes off into brown. The test is delicate down to 1 to 150,000 or less. When a solution is tested and found to be negative, as is the case when hexamethylenamin alone is present, it can be acidulated with sulphuric acid, heated to boiling, cooled off and tested, when the reaction will be positive, due to the breakdown of hexamethylenamin into formaldehyd. This has yielded striking results in the urine, the bile, the sputum, the saliva and the cere-

brospinal fluid, and so contradictory to the generally accepted beliefs that it seemed important to bring them to the attention of the profession. I have thus been diverted from my original purpose, the quantitative estimation of the hexamethylenamin and formaldehyd in the urine. I have at present a promising quantitative method for these determinations and will embody my findings with it in a later communication.

I wish to present here the results of my experiments in regard to the bactericidal powers of hexamethylenamin and formaldehyd, the toleration of the urinary organs to these substances, the question of the excretion of hexamethylenamin in the urine, the bile, the sputum, the saliva and the cerebrospinal fluids. In addition to hexamethylenamin, I have employed helmitol and several other formaldehyd compounds.

Before taking up the actual findings it seems desirable to give a short historical review of the subject.

Hexamethylenamin is formed by the direct action of four molecules of ammonia on six of formaldehyd gas. According to the formula $4\text{NH}_3 + 6\text{HCO} = (\text{CH}_2)_6\text{N}_4 + 6\text{H}_2\text{O}$. It occurs as colorless, odorless crystals, which are ready soluble in water, less so in alcohol. It was first prepared by Butlerow.¹ When acid is added to an aqueous solution there is partial decomposition into formaldehyd and ammonia, and on boiling, complete decomposition. Boiling alone partly causes decomposition. The drug was introduced into medicine as a urinary antiseptic by Nicolaier,² and has ever since enjoyed wide popularity and extensive use all over the world. It remained as a urinary antiseptic alone until S. J. Crowe³ gave it reputation as a gall-bladder and pancreatic disinfectant, and one year later⁴ brought it into its present use as a prophylactic and curative agent in cerebrospinal infections. Armstrong and Goodman,⁵ following Crowe's method, introduced it into use as the disinfectant of the sputum in bronchitis, pneumonia, pulmonary tuberculosis and infections of the nose and throat. After giving it by the mouth, it has been found in the aqueous humor of the eye, in the synovial and pleural fluids. Many clinical contributions of a more or less confirmatory nature have been added and the use of the substance "as a bactericide" in these conditions has grown almost to equal its use as a urinary antiseptic.

TOXICITY OF HEXAMETHYLENAMIN

In the rabbit hexamethylenamin is practically non-toxic. I have given 100 grains at a dose, hyperdermically, without the slightest evidence of poisoning. This animal weighed 2 pounds, so that the equivalent dose in

1. Butlerow: *Liebig's ann. d. Chem. u. Pharm.*, 1860, cxv, 322.

2. Nicolaier: *Deutsch. med. Wchnschr.*, 1895, No. 34.

3. Crowe, S. J.: *Bull. Johns Hopkins Hosp.*, 1908, xix, 109.

4. Crowe, S. J.: *Bull. Johns Hopkins Hosp.*, 1909, xx, 102.

5. Armstrong and Goodman: *Jour. Am. Med. Assn.*, May 27, 1911.

the human being of 150 pounds, would be about 18 ounces. However, there is one marked difference between the human being and the rabbit, i. e., in the rabbit, even on immense doses, there is no decomposition into formaldehyd. The drug is excreted as hexamethylenamin. The toxic effects noted in the human being have been hematuria and vesical irritation, both due to a liberation of formaldehyd gas in the urine at the level of the kidney.

BACTERICIDAL POWERS OF HEXAMETHYLENAMIN AND FORMALDEHYD

The technic employed was uniform, i. e., solutions of varying strength of each drug in sterile water were made. These solutions were then inoculated with the bacteria tested so that a slight clouding of the fluid was produced. The inoculated tubes were then incubated at body temperature in periods varying from a few minutes to a week. The bacteria employed were the colon bacillus, the typhoid bacillus, the bacillus pyocyaneus, the streptococcus and the staphylococcus aureus.

Hexamethylenamin solutions free of formaldehyd were obtained by adding a drop of ammonia to each tube. The hexamethylenamin proved to have no bactericidal power: the organisms tested all lived in from 5 per cent. to 10 per cent. solutions without any deterioration.

The formaldehyd solutions, on the contrary, proved very bactericidal. A solution of 1 to 100 destroyed all the organisms studied in twenty minutes. A 1 to 1,000 solution destroyed all of them within twenty-four hours. Marked differences in the toleration toward formaldehyd was noted between the different bacteria. The most resistant organism was the *Staphylococcus aureus*, and the least resistant, the typhoid bacillus. A solution of 1 to 5,000 formaldehyd destroyed the typhoid bacillus and the streptococcus within twenty-four hours. It destroyed the *Bacillus pyocyaneus* within forty-eight hours, and the colon bacillus in four days. The *Staphylococcus aureus* was still alive at the end of a week. The *Staphylococcus aureus* was completely destroyed in forty-eight hours by a solution of 1 to 2,000 formaldehyd. Solutions of 1 to 20,000 formaldehyd had little or no effect on any of the organisms except the typhoid bacillus and the streptococcus; these were not destroyed at the end of four days, but as shown by reinoculations, were somewhat diminished in vitality. A 1 to 50,000 formaldehyd solution had apparently no effect either in destroying the organism or in inhibiting their growth.⁶

TOXIC EFFECTS OF FORMALDEHYD

In dilutions of 1 per cent. and less, formaldehyd solution is an irritant to the skin: in weaker solutions it is not irritant. Every year there are a few reports of serious poisonings resulting from accidental or

6. All were formaldehyd solutions made from a carefully standardized 10 per cent. aqueous solution of the gas.

suicidal drinking of formaldehyd solutions. In a majority of the cases there are violent gastro-intestinal symptoms, and in the more serious ones, coma, which may last several days. In the fatal cases, death has resulted from gradual paralysis of the cardio-respiratory system. So far as is known to me, there has never been a case in the human being of poisoning from hexamethylenamin due to liberation of formaldehyd in the tissues. Jacobson⁷ states that dogs can take daily 3.2 gm. without serious results. On the other hand, 1 c.c. per kilo is said to be lethal in a single dose. In association with Dr. H. A. Kelly, I have been using, locally, solutions of formaldehyd varying in strength from 1-250 to 1-7,500, in treating infections in various parts of the body, and have never noted any general toxic symptoms.

TOLERANCE OF THE URINARY ORGANS TO FORMALDEHYD

Our method of investigation here was, first, to try various strengths of formaldehyd solution in the bladder, beginning with a very small percentage and gradually increasing it. Having found a solution which was well tolerated in the bladder, it was then injected into the kidney pelvis through a renal catheter. There are marked individual variations in the tolerance of the vesical mucous membrane to formaldehyd solution, and this is independent of the state of inflammation present. Of course, an acutely inflamed bladder is much more intolerant than a healthy bladder. In chronic cystitis and in healthy bladders we have found it practical to use solutions varying in strength from 1 to 3,750, to 1 to 7,500. Occasionally a bladder is met with which does not tolerate even this weak solution. We have had no cases which would not tolerate a 1 to 12,500 solution of formaldehyd. The kidney pelvis will tolerate solutions as strong as does the bladder, and we have never noted any irritation in the kidney itself after an irrigation.

The formaldehyd irrigations for bladder and kidney infections have proved very effectual. They are especially valuable in cystitis, associated with ammoniacal decomposition of the urine, such as occurs with enlarged prostate or tumor of the bladder.

The gall-bladder tolerates formaldehyd readily in solutions of 1 to 3,750. In infected incisions and sinuses, a 2½ per cent. solution can be used without giving undue pain.

A few tests were made with solutions of hexamethylenamin. It is not at all irritating and can be used in the bladder and kidney in 50 per cent. strength without any ill result, but apparently with no effect on the infection.

7. Jacobson: Berl. klin. Wchnschr., 1904, p. 114.

EXCRETION OF HEXAMETHYLENAMIN IN THE URINE

When given by mouth, hexamethylenamin begins to appear in the urine in fifteen minutes, reaches its maximum excretion in two hours, continues to be excreted abundantly for about eight hours, and has, if the dose given was not greater than 30 grains, disappeared in twenty-four hours. After the twelfth hour, the amounts excreted are very small. In a communication to follow this, I will report more in detail the quantitative eliminative amounts of hexamethylenamin.

The question of interest here is, how much formaldehyd is present in the urine after giving hexamethylenamin by mouth? As yet, I have not sufficiently worked out this question, but can say roughly that in some patients it is possible to secure solutions of from 1 to 5,000, and stronger. My important finding was here that on the customary doses, of from 5 to 10 grains, given three times a day, not more than two patients out of ten showed any decomposition of the drug into formaldehyd at all. This was tested out, not only on patients suffering with infections of the urinary tract, but on a series of normal individuals, and on a number of patients convalescent from operations. When a patient was found to show abundant formaldehyd after a 10-grain dose, it also was found that a 2- or 3-grain dose often sufficed to show the breakdown. While not more than 10 per cent. of those examined showed the formaldehyd free after the smaller doses, at least 60 per cent. showed it when the dosage was made from 20 to 30 grains, repeated every four to six hours. In a few instances in which the formaldehyd was not present after dosage of 30 grains, the quantity was raised to as high as 100 grains at a single dose without causing a decomposition of the hexamethylenamin. There are some individuals who do not break down hexamethylenamin into formaldehyd. This, however, is the exception, not the rule.

PLACE OF DECOMPOSITION

At what point in the urinary tract is hexamethylenamin transformed into formaldehyd? In every case in which free formaldehyd was found in the bladder urine and catheterization of the kidney carried out the formaldehyd was found at the level of the kidney. This fact was established in five successive patients. In one patient of this group the blood-serum was examined and found to contain hexamethylenamin, but no formaldehyd. It is my impression that the formaldehyd liberation is due to some specific activity of the renal epithelium. It is, of course, impossible to conceive of free formaldehyd in a highly ammoniacal urine. The urine's alkalinity, however, is normally not due to free ammonia. The greatest decompositions have been observed in highly acid urines. This, however, is not invariably the case, and it was frequently noted that in an acid urine there was no free formaldehyd after giving the hexamethylen-

amin. The same thing holds for alkaline urines. With the reaction definitely alkaline, large amounts of formaldehyd are occasionally met with.

CLINICAL OBSERVATIONS

The clinical results obtained have conformed in every way with the assumption that it is the free formaldehyd which is the effective agent, and that it must be present in fairly strong solution. In not a single case has there been observed the slightest improvement from giving hexamethylenamin when the urine showed hexamethylenamin, but no free formaldehyd. On the contrary, every patient showing free formaldehyd has shown prompt improvement and a number of the very chronic and obstinate colon infections have entirely cleared up. To obtain this result the treatment in some cases had to be carried over several months.

A pertinent example of this kind was afforded by the case of Mrs. E. C. S., aged 29, first seen Oct. 26, 1911. This patient had always been healthy, and had had three normal labors. In March, 1911, when four months pregnant, she was seized with an attack of renal colic in the left kidney region and two days later had a similar one in the right side. She was allowed to continue the pregnancy and gave birth to a healthy child in July, 1911. From the very first attack, the patient began having pus and blood in the urine. This continued after the labor and was associated with irregular fever, marked deterioration of general health and great reduction in hemoglobin. In November, 1911, she had the kidneys catheterized, functional tests made, and (*x*-ray pictures taken) collargol injection of the pelves. The results of these examinations were to show that there was bilateral colon bacillus infection of the kidneys, greatly dilated pelves, the left having a capacity of 120 c.c. and the right of 320. The functions of the kidneys, however, were fairly well maintained, as shown by the phenolsulphonaphthalein test. Ten grains of hexamethylenamin by mouth sufficed to give free formaldehyd from both kidneys. At the time of the examination there was an enormous amount of pus on both sides. The patient was started on 120 grains of hexamethylenamin per diem. This occasionally caused vesical distress, when the dose was reduced. By February 3, the urine had practically cleared of infection. On that date Dr. Kelly suspended and plicated the pelvis of the right kidney. On the twentieth of the same month a similar operation was carried out on the left side. The hexamethylenamin was continued during her stay in the hospital. A recent examination shows a perfectly sterile urine, free from pus and blood.

THE DOSAGE OF HEXAMETHYLENAMIN

The average dose advised for hexamethylenamin is 7.5 grains, repeated two or three times per diem. In an occasional case of irritable bladder, even this amount causes a sufficient liberation of formaldehyd to produce irritation. Such, however, is the exception. If it does cause irritation, free formaldehyd will always be found and the indication is to reduce the dose. From what has been said, it is evident that there is no fixed dose. This is to be obtained by testing the urine and observing the toleration of the patient. Where 10 grains causes no free formaldehyd liberation, the dose should be increased to 20 grains, and if there is still none, to 30 or 40 grains, repeated every four hours. The only toxic effect due to

hexamethylenamin is occasioned by the liberation of formaldehyd in the urine, and when this does not occur, it is safe to push the dose until it does appear. The first disagreeable symptom in our experience is vesical irritability. It has always led us to discontinue or diminish the dose. In such a case, pushing the dose might easily lead to hematuria. We have never observed a macroscopic hematuria from the use of hexamethylenamin.

The proper treatment is to give a dose just large enough to be under that necessary to cause bladder irritation. Using this dose, improvement will follow so rapidly in most cases that long continuation in the use of the drug is unnecessary. On the other hand, it is certainly possible to keep up the dosage for months without any serious impairment of either the general health or of the kidneys.

SOME OF THE PROPRIETARY HEXAMETHYLENAMIN COMPOUNDS

The first trade name and one which has been so universally used as to have become fixed in the popular mind is urotropin. It is, however, sold under various other names, such as formin, cystamin, hexamin, etc. These products are identical with hexamethylenamin and show no variations from it in chemical or pharmacologic reaction.

Helmitol, the methylene citrate of hexamethylenamin, also responds like the pure drug. There is this difference, however: When hexamethylenamin is dissolved in water no free formaldehyd is formed; when helmitol is dissolved in water a considerable amount of free formaldehyd is liberated. Formaldehyd, however, when taken by the mouth, is not excreted through the kidneys. When helmitol is taken, its excretion is identical with that of hexamethylenamin; i. e., in some cases, there is free formaldehyd liberated, and in others, none.

COMBINATION OF DRUGS WITH HEXAMETHYLENAMIN

In the hope that the presence of some other substance in the urine would cause decomposition of the hexamethylenamin, a great variety of substances have been given with it. Among these are potassium citrate, potassium iodid, sodium benzoate, salol, oil of wintergreen, etc. The results have not been encouraging; in no instance has the combination been more effective than the pure drug.

OTHER FORMALDEHYD-CONTAINING DRUGS

Dr. H. A. B. Dunning has furnished me with a number of formaldehyd compounds, some of them new ones; some of them have been excreted through the kidneys as in the case of a compound between formaldehyd and phenolsulphonephthalein. None, however, has shown a tendency to break down, liberating free formaldehyd. This phase of the subject is still under investigation.

EXPERIMENTAL STUDIES WITH RABBITS

The use of hexamethylenamin in rabbits was carried out in order to determine its toxicity and its method of excretion. Only three animals were employed. The results obtained were identical. In the rabbit, hexamethylenamin is excreted primarily and principally through the kidneys. It is excreted unchanged, and is not broken down into formaldehyd. In small doses of from 2 to 5 grains, hypodermically, in a 2-pound rabbit, the excretion is practically entirely through the kidneys. When from 30 to 100 grains are given at a dose, the principal excretion is through the kidneys, but there is a large excretion through the bile. The drug is eliminated as hexamethylenamin, there being no formaldehyd liberated. The hexamethylenamin does not seem in the least toxic to the rabbit.

When a rabbit is given 30 grains of the drug hypodermically and then killed within an hour the findings in the different tissues are as follows: Urine, large amount; bile, considerable amount; cerebrospinal system, traces; blood, considerable amount; spleen, liver and kidneys, considerable amount; muscles, trace; skin, trace; in no tissue was any free formaldehyd found. These findings in the tissues and body fluids of the rabbit suggested the examination of some of the fluids of the human being where the drug has been thought to act efficiently.

EXAMINATION OF THE BILE

I examined in all ten patients with biliary fistula. None of them were getting less than 60 grains a day, and in one case I gave 100 grains at a dose and collected the bile for twelve hours. The bile in every case was treated identically, i. e., it was diluted slightly with distilled water, acidulated with sulphuric acid, and distilled. In every case the distillate gave a clear formaldehyd reaction with Hehner's test. In not one could a trace be found by the test which I have employed.

As a control, I put a solution of 1 to 50,000 hexamethylenamin into bile, allowed it to stand an hour and then distilled. The presence of formaldehyd was easily determined and there seemed to be an actual concentration in the distillate.

EXAMINATIONS OF THE SPUTUM AND SALIVA

In five healthy people I gave hexamethylenamin in 30-grain doses, at the rate of 120 grains a day for twenty-four hours, and then examined the saliva. By the Hehner test, either hexamethylenamin or formaldehyd was found to be present. By the phenolhydrazin-sodium-nitroprussid test, neither could be detected.

In three cases of bronchitis with mucopurulent expectoration, exactly similar technic was followed with identical results. By my test there was no free formaldehyd, and heating and acidulating proved that there was no free hexamethylenamin in amount sufficient to give the reaction.

EXAMINATION OF THE CEREBROSPINAL FLUID

The cerebrospinal fluid was examined in one case through the courtesy of Dr. Morse, of the Johns Hopkins Hospital staff. The patient, James B. D., aged 45, had normal temperature and no cerebral or spinal symptoms. For purposes of diagnosis, some of his cerebrospinal fluid was desired. Before the puncture he had been given, for twenty-four hours, 15 grains of hexamethylenamin every three hours. I obtained about 4 c.c. of clear fluid which showed a positive reaction with Hehner's test, but none whatever with the other test, even when boiled and acidulated.

CONCLUSIONS

These examinations of the bile, sputum, saliva and cerebrospinal fluid show that even after rather large doses of hexamethylenamin, there appears in them but traces of the drug, certainly in percentages less than 1 to 150,000. Whether this trace is of hexamethylenamin, as seems most likely, or of formaldehyd, it is impossible to state, because the only test which would show it is Hehner's which does not differentiate these two substances. So far as any therapeutic value is concerned, it does not make any difference because, as already shown, solutions of formaldehyd of the weakness indicated, do not possess any antiseptic value. I believe, therefore, that the use of hexamethylenamin for the curing or bettering of, or as a prophylactic against, infections of the bile passages, respiratory passages and cerebrospinal system is illusory, and cannot possibly yield results. I have no explanation to offer for the reported clinical and bacteriologic improvements, for with the exception of the urine, I have not tested this side of the question. In the urine the clinical and bacteriologic findings have conformed in every way with the chemical findings, viz., only those patients who show free formaldehyd have been improved by the drug.

The phenolhydrazin-nitroprussid test is very simple, and when applied gives the physician an easy method of determining the dose of hexamethylenamin which he should use, and also shows those cases in which no results from this drug can be expected.

The test is of value in determining the efficiency of compounds whose value rests on the liberation of free formaldehyd, and it is to be hoped that an endeavor will be successful in securing a substance which, when taken by the mouth, will be excreted through the kidneys and will liberate formaldehyd in the urine in every case.

Although it has its limitations, these experiences show that hexamethylenamin, when properly given, in more than a half the cases of urinary infection is of immense value, and at the present time superior to any other drug in common use.

Finally, I want to express my gratitude for the enthusiastic support and many valuable suggestions given me by Dr. Howard A. Kelly during the progress of this work.

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COMPLETE AND PERMANENT HEART-BLOCK FOLLOWING THE USE OF DIGITALIS IN AURICULAR FIBRILLATION *

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One of the commonest, as well as one of the most interesting, varieties of cardiac irregularity is that known as auricular fibrillation. In this condition the auricles, instead of contracting rhythmically, are thrown into a state of tremulousness involving small bundles of fibrils.

The walls of the auricle stand in the diastolic position; systole, either complete or partial, is never accomplished; the wall, as a whole, is stationary, but careful examination of the muscle reveals an extremely active condition; it appears to be alive with movement; rapid, minute and constant twitchings or undulatory movements are observed in a multitude of small areas upon its surface (Lewis).

The result, usually, is a rapid and extremely irregular pulse. From the turmoil in the auricles a shower of impulses passes down the bundle of His into the ventricles. The weakest of these impulses fail to affect the ventricles. The stronger ones, occurring at irregular intervals, cause ventricular systole and lead to the production of what used to be known as the *pulsus irregularis perpetuus* (Hering) or *arrhythmia perpetua* (Gerhardt). These terms are not accurate since the condition is occasionally compatible with a regular pulse and, while usually permanent, may be transient (Mackenzie, Hewlett and Barringer, Fox and others).

The venous pulse, in these cases, is characteristic and from it the diagnosis can readily be made. The *a* wave disappears entirely from the jugular sphygmogram and the same is true of the esophageal tracing (Hewlett) and the electrocardiogram (Hering). Whenever the diastole is somewhat prolonged, a series of fine wavelets may often be seen in the venous sphygmogram (Figs. 5 and 6). Mackenzie was at first inclined to consider these as artefacts, but since they correspond in their rate with similar waves in the electrocardiogram, he now agrees with most other observers that there is reason to suppose them an expression of the auricular tremor.

While in most cases of auricular fibrillation, the pulse is rapid and irregular, it need be neither. In his classical monograph on Nodal Bradycardia, Mackenzie has reported a considerable number of cases of this sort

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in some of which the pulse was slow and irregular, in others slow and regular. Gibson, Lewis and others have reported similar cases. A seductive theory, in explanation of this phenomenon, has been advanced by Lewis. He considers the occurrence of a slow pulse in auricular fibrillation to be an expression of an impaired conductivity on the part of the auriculo-ventricular bundle. If the heart-block is partial, an occasional tremor only goes through and causes ventricular systole. The result is a slow and irregular pulse, sometimes with long pauses. If the block is complete, the fibrillating auricles can no longer affect the ventricles. The latter establish their own rhythm and beat slowly and regularly as in an ordinary case of complete heart-block. From the nature of the case, the validity of this explanation cannot be established in every instance. But, as Lewis has pointed out, one at least of Mackenzie's cases strongly supports this view. The patient, a subject of rheumatic fever, was known to have had impairment of conductivity, in greater or lesser degree, for twelve years. He then suddenly developed slow and irregular action of the heart, with evidence of auricular fibrillation. This lasted a week, at the end of which time both auricles and ventricles again resumed their rhythmic action, but with an *a-v* interval twice as long as normal. Several months later, the slow and irregular pulse, with auricular fibrillation, returned and thereafter persisted. Gibson has reported an equally instructive case. The first tracings obtained were those of ordinary partial heart-block, with an auricular rate of 168 and a ventricular of 42. On one occasion auricular fibrillation set in, with an irregular but still phenomenally slow pulse. A post-mortem examination revealed an increase in the fibrous tissue of the *a-v* bundle with wide separation of the fibers composing it. Lewis and Mack have reported a case of auricular fibrillation in which the ventricles beat regularly at a rate of 30 per minute. By means of the electrocardiograph they showed that the impulses from the fibrillating auricles were not transmitted to the ventricles and that the impulses originating the rhythm of the latter started at a point in the ventricular wall not far removed from the auriculo-ventricular ring. There is thus good reason to suppose that the slow pulse occasionally seen in auricular fibrillation is due to partial or complete heart-block, as the case may be.

Mackenzie has shown that digitalis slows the pulse far more readily and to a far greater extent in auricular fibrillation than in any other cardiac condition, with the exception of cases of partial heart-block. This phenomenon can readily be observed by anyone who studies this condition. Lewis was the first to suggest the theory that here, too, the slowing produced by the administration of digitalis is due to the production by this drug of a partial or complete heart-block, thus preventing the passage of some or all of the fibrillation impulses at the *a-v* junction.

It is well-known that digitalis, either through the vagus or directly or both, often depresses the conductivity of the bundle of His. This is especially the case where the conductivity of the bundle has already been impaired by some organic lesion. Thus cases of partial heart-block are nearly always aggravated by digitalis and the case of Windle, in which heart-block was apparently produced *de novo* by the administration of digitalis, was one of rheumatic mitral disease, in which an impairment of the conductivity of the bundle is not infrequently found. Similarly Mackenzie has shown that of cases of auricular fibrillation, those which are of rheumatic origin or those in which mitral stenosis is present, are most susceptible to digitalis. It is therefore reasonable to suppose, that in these cases we have, besides the auricular fibrillation, a pre-existing impairment of conductivity and that digitalis here produces its exceptionally great retardation of the pulse by still further depressing the conductivity of the already organically diseased bundle. Further clinical and, if possible, experimental evidence is needed to prove the validity of this theory in all cases. It is believed that the second case, to be reported below, may be of value in this connection.

In all cases hitherto reported, in which digitalis has slowed the pulse in auricular fibrillation, the action of the drug has been temporary. Even when the slow, regular pulse of complete heart-block has been produced, a discontinuance of the drug has been followed by a return of the rapid, irregular pulse characteristic of uninfluenced auricular fibrillation. That this need not always be the case, it is the object of this communication to show. It would seem, from the two cases to be related below, that occasionally the depression produced by digitalis in the conductivity of the diseased bundle may result in a permanent injury to the latter, leading to the production of a complete and permanent heart-block with its characteristic regular and extremely slow pulse. They further seem to show that this is an eminently undesirable accident, since in both patients the condition, after the establishment of the complete block, was far worse than before and death ensued in ten and sixty-four days, respectively.

CASE 1.—Male, aged 80 years. No rheumatism, syphilis or alcoholism. In 1868, while suffering from a severe laryngitis, he had a sudden attack of syncope in which he thought he was dying. He felt well the next day, but soon after began to have periods of dyspnea on slight exertion, which slowly grew more frequent and more severe. He did not consult a physician but twenty years later they had become so harassing, coming on once a month or oftener and lasting several days, that he retired from business. Since 1906 he had been more or less of an invalid—weak, dyspneic, with periods of cardiac palpitation and occasional precordial pain. His feet and legs became edematous and continued so until I saw him in 1908. I found him with an enormously dilated heart, mitral and aortic regurgitation; marked arteriosclerosis, congested and ptotic liver, great edema of legs, rapid and irregular pulse, urine scanty with albumin and casts. The usual treatment led to a gradual amelioration of his symptoms. Every few months thereafter, he had a relapse, which always yielded promptly to digitalis.

In April, 1910, I began to study his pulse with the Jaquet cardio-sphygmograph, which showed the condition to be one of auricular fibrillation. On June 21, having been without medication for some time, his pulse was irregular, averaging 70 beats per minute with occasional bigeminy and with the jugular pulse of auricular fibrillation (Fig. 1). Under digitalis (digalen 1 c.c. t.i.d.), his pulse became very slow (38 per minute) and nearly regular (Fig. 2) without subjective improvement. The digitalis was discontinued but the heart-block pulse persisted (Fig. 3), dropping to 33 beats per minute on July 5, and continuing unchanged until his sudden death on July 8. An autopsy was refused.

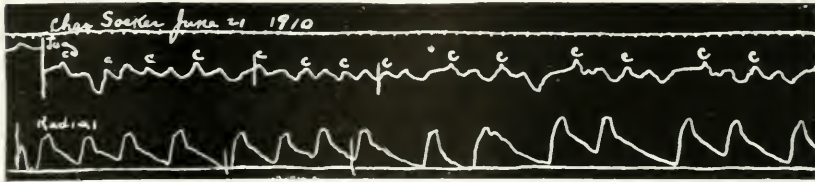


Fig. 1.—Jugular and radial pulse showing auricular fibrillation uninfluenced by digitalis.

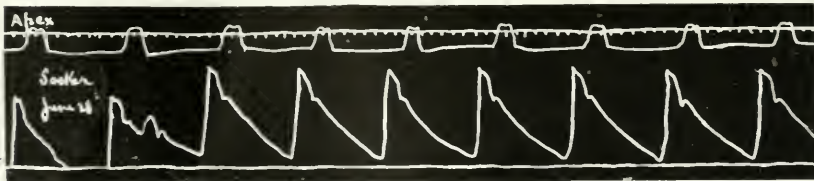


Fig. 2.—Apex beat and radial pulse after a week of digitalis. Note typical heart-block pulse. The irregularity in the second pulse beat is due to a movement of the patient's hand.



Fig. 3.—Jugular and radial tracing, one week after digitalis was discontinued. The jugular pulse shows auricular fibrillation, the radial complete heart-block.

We have here, then, a case of auricular fibrillation in which a moderate dose of digitalis produced complete auriculo-ventricular block, the latter persisting until the patient died, ten days after the discontinuance of the digitalis.

CASE 2.—Male, aged 58 years, was admitted to the Washington University Hospital, service of Dr. George Dock, on Dec. 8, 1911. Besides the usual diseases of childhood, he had had pneumonia at the age of 28 years, and meningitis at 49 years. There was no history of rheumatism or of syphilis, but a definite one of long continued alcoholism. In June, 1910, he was severely injured about the head. The accident was followed by a series of convulsions, very suggestive of

epilepsy and recurring at irregular intervals up to the time of his death nearly two years later. During some of these he bit his tongue and otherwise injured himself. In October, 1910, he first noticed evidence of cardiac incompetence: dyspnea and cardiac palpitation, varying in intensity, but on the whole growing steadily worse until he entered the hospital on December 8, 1911. At this time, the heart was found moderately enlarged, with evidence of dilatation of the left auricle and very irregular action. A low-pitched murmur was audible over the apex, beginning just after the second sound and occupying the first portion of diastole. When the latter was long, a distinct interval of silence could be made out between the end of the murmur and the beginning of the first sound. There was some pulmonary edema but none of the feet. The liver was not enlarged. The maximal blood-pressure varied from 110 to 140 mm. Hg, according to the strength of the individual cardiac contractions, the minimal pressure being about 90 mm. The jugular and radial tracings showed the presence of auricular fibrillation (Fig. 4), confirming the evidence of the murmur, which was identical with that described by Mackenzie as characteristic of mitral stenosis when coexisting with auricular fibrillation.

Digitalis was given, at first tentatively, but later, when this seemed ineffective, in doses of 1 c.c. of the tincture every four hours. No marked effect was produced until eight doses had been given. Then, at midnight, the resident, Dr. Brotherhood, was called, as the patient was in convulsions. He found the pulse 40 beats per minute with long periods of asystole and ordered the digitalis discontinued.

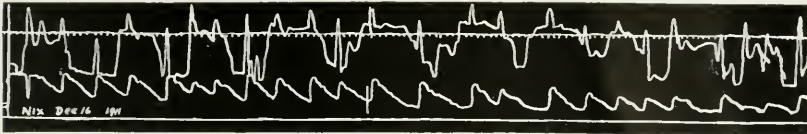


Fig. 4.—Jugular and radial pulse uninfluenced by digitalis. Auricular fibrillation.

The next day the patient seemed weak but was not carefully observed. On the following day, however, he went from one convulsion into another, each lasting a minute or two, apparently accompanied by hallucinations and followed by a brief period of confusion. There was no dyspnea or cyanosis. The pulse was very slow but strong, with frequent intermissions, sometimes lasting several seconds, and very suggestive of heart-block (Fig. 5, 6 and 7). It sometimes seemed as though a seizure were preceded by an unusually long intermission, but of this I was not quite sure. It was impossible to feel or record the pulse during an attack on account of the violence of his motions. The cardiac outlines and sounds did not differ from those previously recorded. Atropin sulphate gr. 1/60 hypodermically produced no effect on the pulse. This same day (December 20) the patient was taken home, where I saw him thereafter at frequent intervals. On December 20 the pulse was nearly regular, 20 beats per minute, still with the jugular pulse of auricular fibrillation (Fig. 8). On the following day the pulse became entirely regular and, from this time until his death on February 23, the cardiac condition was unchanged.

The pulse remained very slow, varying between 30 and 40 beats per minute, entirely regular except for rare extra-systoles; many tracings were taken from time to time, of which two are here reproduced (Figs. 9 and 10). The cardiac dulness and the murmur remained unchanged. From week to week, the dyspnea increased but there was never any evident cyanosis. The convulsions came on frequently and at irregular intervals, the latter sometimes being a week or more in duration. No difference in the pulse could be noted between the convulsive and non-convulsive periods. Frequent attempts were made to influence the pulse by

swallowing, pressure on the vagi, large doses of atropin and of digitalis, but no effect could ever be noted. The blood-pressure remained of the heart-block type, the maximal pressure averaging 195 mm. Hg, the minimal 60 mm. On February 23 he died, with no change in his condition except a progressive weakness and dyspnea. Until a minute or two before his death, that is as long as the pulse could be felt, it maintained its slow, regular rhythm. An autopsy was performed a few hours after death, by Dr. George M. Smith of the pathologic department of Washington University.

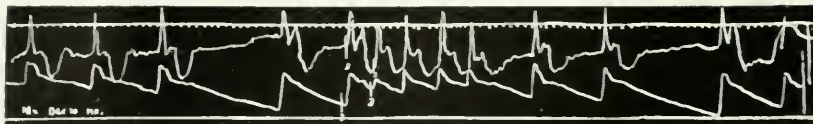


Fig. 5.

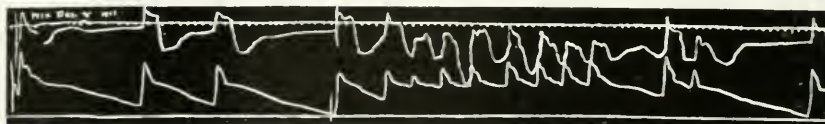


Fig. 6.

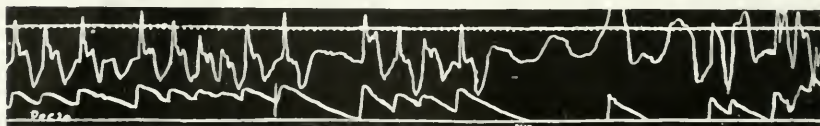


Fig. 7.

Figs. 5, 6 and 7. Jugular and radial pulse, 24 hours after digitalis was discontinued. Auricular fibrillation. The occasional long pauses between beats are suggestive of partial heart-block. In Fig. 7, two respirations are recorded in the jugular pulse during a period of asystole. During this and the following diastole the blood-pressure fell so greatly that the collapsing radial allowed the writing point to leave the paper.

The following is an abstract of the pathologic findings, a more detailed account of which will appear elsewhere:

Anatomical Diagnosis.—Valvular disease of the heart; mitral stenosis; fibrous myocarditis. General arterial sclerosis; calcification of part of ventricular septum causing destruction of auriculoventricular bundle; edema of lungs, chronic pleuritis (right); chronic passive congestion of lungs, liver, spleen and kidney; ascites; porencephalus.

Two small cysts, probably caused by old hemorrhages, were found at base of the occipital lobes. Brain otherwise was normal. Sections from the cortex of the motor area showed no changes.

Weight of heart 317 grams. Moderate hypertrophy of both ventricles. Dilatation of both auricles. Thrombus was found in the wall of the left auricle. Both mitral leaflets were much thickened and produced a contraction of the mitral orifice so that this barely admitted the tip of the little finger. At the base of the

aortic leaflet of the mitral valve there was a large irregular calcareous mass extending over into the ventricular septum. This nodule met and practically destroyed the auriculo-ventricular bundle just anterior to the septum membranaceum before the bifurcation of the bundle had occurred. The microscopic sections exhibiting the maximum point of injury showed that merely a few scattered muscle fibers still remained. The node of Keith and Flack contained a considerable amount of fibrous tissue.

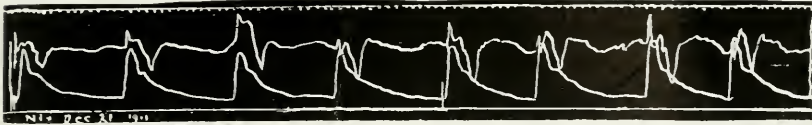


Fig. 8.—The pulse has become comparatively regular and very slow, suggesting nearly complete heart-block. As in all the tracings, the jugular pulse shows that the auricle is fibrillating.

This case presents several points of interest. Tracings 5, 6 and 7 seem clearly to show the onset of partial heart-block following the administration of digitalis. Tracing 8 shows evidence of nearly complete block on the following day. This, as indicated by Tracings 9 and 10, became

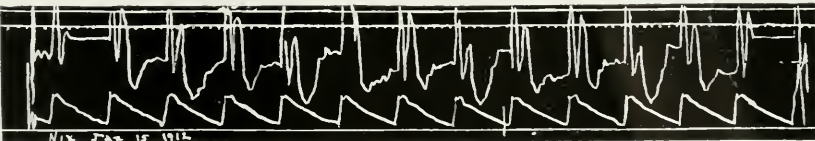


Fig. 9.

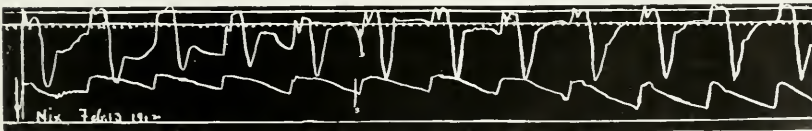


Fig. 10.

Figs. 9 and 10.—Two examples of nearly daily tracings taken between the onset of complete heart-block on December 21, and death on February 23. All show continued auricular fibrillation in the jugular pulse and evidence of complete heart-block in the radial.

complete and remained permanent. The fact that neither vagal stimulation, atropin or digitalis affected the block, is evidence that the latter was not functional but organic, and this conclusion is borne out by the pathologic findings.

The conclusion thus seems justified that we had here a heart with an anatomically impaired auriculo-ventricular bundle, but one still competent to transmit auricular impulses; the digitalis, by still further depressing

its conductivity, administered the *coup de grâce* to the diseased bundle and led to its complete and permanent obliteration. It is possible, of course, that the block was entirely due to the gradual extension of the anatomic lesion of the *a-v* bundle, which at this moment happened to interrupt its continuity, at first nearly and then quite completely, independently of the digitalis, and that the administration of the latter was merely a coincidence. The fact, however, that the phenomenon followed the use of digitalis in two cases renders this hypothesis less probable than the other.

Whether the patient's convulsions were due to the bradycardia remains problematic. Some of them were certainly epileptic and perhaps all of them were so. It may be that the cerebral anemia, resulting from the block, stimulated the brain to the production of an increased number of epileptic seizures.

It is a pleasant duty to thank my honored chief, Dr. George Dock, for permission to report this case and for the interest shown during its study.

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THE ADRENAL GLANDS AND BLOOD-PRESSURE *

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The first significant contribution to the function of the adrenal glands was made by Addison, when, in 1855, he discovered their relation to the disease which bears his name. Stimulated by this discovery, Brown-Séquard the following year succeeded in demonstrating that removal of both glands in an experimental animal leads to a marked asthenia of the muscular structures of the body such as characterizes Addison's disease. In 1895 Oliver and Shaefer showed that adrenal extract has a powerful effect on blood-pressure—a fact that was independently discovered by Cybulski and Szymonowicz. It has since been shown that this effect is produced by extracts of the medullary portion of the gland only. It is shared, however, by extracts of chromaffin tissue wherever found.¹

Probably the most significant discovery of recent years is that the injection of adrenal extract is exactly equivalent to stimulation of the sympathetic (thoracico-lumbar autonomic) nervous system. The result of such injection depends in any organ on its sympathetic innervation. If it has no sympathetic fibers no effect is produced. If such fibers are present the effect is stimulation or depression, depending on which function is mediated by these fibers. Finally, in an organ in which sympathetic impulses are infrequent the injection has correspondingly slight effect.² Recent researches at the Harvard Medical School³ have shown that during periods of particular stress the adrenals are stimulated to an augmented secretion which reinforces the sympathetic activity characteristic of such periods. In cats under the influence of anger or fear, partial asphyxia and strong sensory stimulation epinephrinemia has been demonstrated.

The idea very generally obtains that an important function of the chromaffin tissue is to maintain a constant tonic activity in the sympathetic system. Whether, however, such influence is mediated during periods of ordinary quiet existence is questionable. The theory is based largely on an assumption that minimal quantities of circulating epinephrin have an effect qualitatively similar to that of the comparatively

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1. For an excellent detailed review of the literature on the adrenals see Vincent; *Ergebn. d. Physiol.*, 1910, ix, 509.

2. Elliott; *Jour. Physiol.*, 1905, xxxii, 401.

3. Cannon and de la Paz; *Am. Jour. Physiol.*, 1911, xxviii, 64. Cannon and Hoskins, *Am. Jour. Physiol.*, 1911, xxix, 274.

enormous quantities that have usually been employed in experimental investigations. Such an assumption is not necessarily true. It is possible that the threshold of stimulation is sufficiently high not to be reached by the ordinary concentration of circulating epinephrin. That different quantities of epinephrin may have different effects is shown by the fact that in the small intestine a stimulating effect of epinephrin has been noted when very dilute solutions are used, whereas the effect of stronger solutions is depression.⁴ A similar reversal of reaction has been noted recently by Stewart⁵ when very dilute solutions are applied to uterine tissue.

In view of the fact that the sympathetic nervous system has an important regulatory influence in the so-called "vital functions," it is a question of considerable moment whether the adrenals actually do have the assumed tonic influence on this system. If so, the vital activities must constantly fluctuate with variations in the activity of the glands. Any diagnosis, then, that fails to take them directly into account is to that extent inadequate. Similarly, if they have such an important function, every autopsy should include not only a careful microscopic examination of the glands, but also a physiologic determination of the potency of their chromaffin tissue. If the tonic activity of the sympathetic system does depend on these organs their functioning must be a major factor in the physiologic régime as well as in many symptom complexes.

There is, however, as previously indicated, a possibility that the peculiar relationship subsisting between the chromaffin tissue and the sympathetic system is of utility only during periods of special stress. In that event there would ordinarily be no probable error introduced in diagnosis by a failure to consider the adrenals.

Of the bodily functions controlled by the sympathetics, blood-pressure is supposedly one of the most sensitive to epinephrin. For this reason and on account of the ease with which blood-pressure can be recorded, studies of the relation of the adrenals to the sympathetics can well be made on the vasomotor system. Possibly the two best known facts regarding the physiology of the adrenals are that their deficiency causes vascular hypotension, while, on the other hand, injection of epinephrin causes a marked hypertension. There are two possible factors in this hypertension—increased vasoconstriction and augmented heart beat. The latter factor is frequently masked by a cardiac inhibition mediated by the vagus nerve—a reflex reaction to the increased blood-pressure following vasoconstriction. It is not to be supposed, however, that the cardiac stimulation is in abeyance; a similar vasoconstriction without the

4. Hoskins: *Am. Jour. Physiol.*, 1912, xxix, 363.

5. Stewart: *Jour. Exp. Med.*, 1912, xv, 517.

supporting epinephrin stimulus to the heart would lead to a considerably greater cardiac inhibition with correspondingly smaller elevation of pressure.

EFFECTS OF EXPERIMENTAL ADRENAL DEFICIENCY

A condition of adrenal deficiency can be obtained experimentally by extirpating the glands or by occluding their circulation; these procedures give a condition of extreme, though not absolute, chromaffin deficiency. As to the ultimate effects of such experiments there is no question. Within a few hours to a few days there develops an asthenia which is shared by the musculature of the circulatory system and leads to extreme vascular hypotension. As to the immediate effects, however, the evidence is not concordant. A number of investigators have studied the effects of tying off the adrenal vessels while blood-pressure was being recorded. Strehl and Weiss⁶ noted in rabbits a fall of pressure immediately succeeding such ligation, followed by an immediate rise when the ligatures were released. But Young and Lehman,⁷ performing the same experiment on dogs, observed on ligation but little fall, and that occurred very gradually. When the ligatures were released there followed, in three of their eight experiments, a decided rise of pressure: in two, a slight rise and in three, no effect. Young,⁸ who subsequently repeated the work, observed no significant fall of pressure for hours after tying off the glands. Similar negative results have been obtained by Kahn⁹ in rabbits, and by Hoskins and McClure¹⁰ in dogs.

That circulating epinephrin is quickly destroyed is well known. If, therefore, the adrenals by their secretion exert a constant tonic influence on the sympathetic system, ligating off the glands should result in an immediate fall of pressure. The failure of such a result militates against the view that a tonic influence exists. It is to be noted that in such experiments the effects of making the occlusions alone are significant. Whether or not a subsequent rise occurs when the vessels are released, means little. Checking the circulation in any given case might result either in a long continued depression of the glands such as occurs in the kidney after occlusion of the renal vein, or in an accumulation of elaborated secretion. Consequently, releasing the vessels would not be at all likely to restore normal conditions and any effect produced would not be intelligible.

6. Strehl and Weiss: *Arch. f. d. ges. Physiol.*, 1901, lxxxvi, 107.

7. Young and Lehman: *Jour. Physiol.*, 1908, xxxvii, p. liv.

8. Young: Cited by Vincent (Note 1).

9. Kahn: *Arch. f. d. ges. Physiol.*, 1911, cxl, 216.

10. Hoskins and McClure: *Am. Jour. Physiol.*, 1912, xxx, 192.

EFFECTS OF INJECTING EPINEPHRIN

Another method of investigating the relation of the adrenals to blood-pressure is to determine at what rate epinephrin must be injected into the blood-stream of an animal to cause a minimal rise of pressure, and compare this with the actual rate of secretion by the adrenal glands. Very little work apparently has been done along this line, but Lewandowski has observed that the injection into an experimental animal of blood from the adrenal veins, at the rate at which it normally flows, has no effect on blood-pressure.¹ The proposed plan of procedure at once raises several questions: What is the concentration of epinephrin in the blood in the adrenal veins? What is the rate of blood-flow in these veins? Is there normally an accumulation of epinephrin in the blood-stream sufficient to maintain a concentration above the threshold value for sympathetic stimulation?

As to the concentration of epinephrin in adrenal blood, Ehrmann,¹¹ using the enucleated frog's eye as a test object, found in the rabbit a value of 1:1,000,000 to 1:10,000,000. Watterman and Smit,¹² however, having noted that fresh serum causes mydriasis independent of its epinephrin content, thought Ehrmann's values too high. Making similar determinations after keeping the serum for twenty-four hours on ice, they found a mydriasis corresponding to that of an epinephrin solution of 1:10,000,000. This they regarded as the normal concentration. More recently, O'Connor,¹³ with better technic, using Trendelenburg's frog perfusion method, has found epinephrin in plasma from the rabbit's adrenal veins in concentration of 1:1,000,000 to 1:5,000,000. Stewart⁵ has recently reported an instance in which he was unable to detect epinephrin in the adrenal blood of a dog.

In order to avoid as far as possible abnormal experimental conditions, we attempted first to determine in the dog somewhat indirectly the adrenal output. Cannon and de la Paz³ have described a method of obtaining samples of blood by inserting a flexible catheter through the femoral vein into the vena cava to the adrenal region. We hoped to be able to demonstrate in blood so collected an epinephrin content enough higher than that of ordinary venous blood to permit a determination of the difference. Then, by allowing for subsequent dilution in the heart, and considering the rate of general blood-flow we might calculate the rate of epinephrin secretion. But the quantity secreted proved too minute for detection by the rabbit intestine method (described below) which was used. It was proved, however, that there is a difference of less than 1:100,000,000 in the epinephrin content of blood from the vena cava at

11. Ehrmann: *Arch. f. Exper. Path. u. Pharm.*, 1905, iv, 39.

12. Watterman and Smit: *Arch. f. d. ges. Physiol.*, 1908, cxiv, 198.

13. O'Connor: *Arch. f. exper. Path. u. Pharm.*, 1910, lxiii, 161.

the mouths of the lumbo-adrenal veins and that from the femoral vein. These results indicate roughly that there is in the arterial blood as it leaves the heart at most, less than one part of epinephrin in 200,000,000.

Being unsuccessful in these attempts, we then made a number of direct determinations of the epinephrin content of the blood from the lumbo-adrenal veins. The blood was collected by a method that has been used by a number of other investigators. The animals were etherized, then, while the viscera were protected by warm towels, the vena cava and

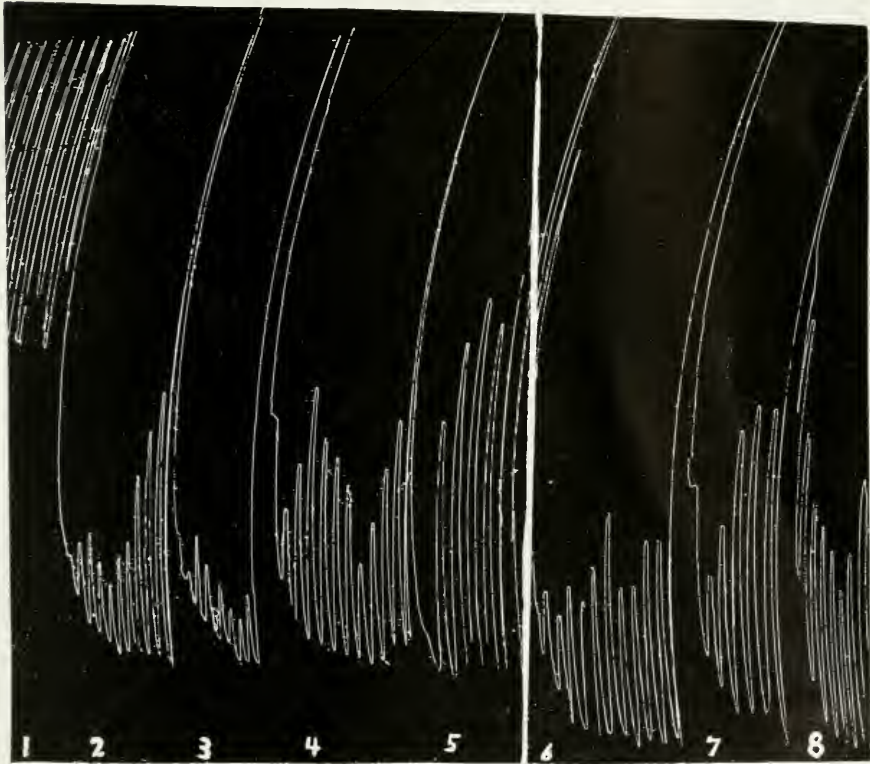


Fig. 1.—Epinephrin content of blood from adrenal veins. Segment of rabbit intestine beating in: 1. Blood from femoral vein. 2. Blood from adrenal vein. 3. Adrenalin 1:4,000,000. 4. Blood from adrenal vein. 5. Adrenalin 1:8,000,000. 6. Adrenalin 1:6,000,000. 7. Adrenalin 1:7,000,000. 8. Blood from adrenal vein. Blood diluted four times. Adrenalin solutions in blood from femoral vein similarly diluted.

aorta were ligated posterior to the renal veins; the renal veins were ligated at the hilus of each kidney. Then an oiled right angle glass cannula was inserted into one renal vein so as to drain the vena cava, which was finally occluded by a hemostat anterior to the mouths of the lumbo-adrenal veins. Care was taken to avoid massaging the adrenal glands.

The blood that had collected during the final stages of the procedure was carefully pressed out through the cannula, which was then elevated a few centimeters to simulate normal pressure. After the vena cava had refilled and blood-flow was reestablished through the cannula a three-minutes sample was taken for tests. Previous to this about 25 c.c. of blood was withdrawn from the femoral vein to serve as a "standard." The blood in each case was defibrinated by beating as it flowed.

TABLE I.—OUTPUT OF EPINEPHRIN FROM ADRENAL GLANDS OF DOGS

Dog	Weight, Kilos	Rate of Blood Flow c.c. per Minute	Epinephrin Content	Output per Dog per Minute*	Output per Kilo per Minute*
A	10.0	8.0	1:2,500,000	3.0	0.3
B	5.2	3.0	1:2,000,000	1.5	0.3
C	15.0	16.0	1:4,500,000	3.5	0.23
D	13.4	21.0	1:4,000,000	5.0	0.37
E	13.5	13.0	1:8,000,000	1.5	0.8
Aver.	11.4	12.2	1:4,200,000	2.5	0.25

*The figures in this column represent c.c. of 1:1,000,000 solution.

To determine the epinephrin content we employed the rabbit intestine method as previously described by Hoskins.¹⁴ The method, in brief, consists of applying the blood to be tested to a segment of rabbit intestine rhythmically beating in defibrinated blood from the femoral vein. A depression of the tonus and the rhythmic activity of the segment occurs proportional to the quantity of epinephrin present. The segment used is "calibrated" in each instance by noting the effects of known concentrations of epinephrin in the "standard" blood. In the use of the intestine method better results are usually obtained if the blood is diluted two to four times. In ordinary blood there is a stimulating substance that may act so strongly as seriously to interfere with the reaction to epinephrin. In the experiments herein reported "adrenalin" (Parke, Davis & Co.) was used as standard epinephrin.

In such experiments, incidentally, blood must always be used as standard. Much confusion in the literature has arisen from attempts to compare blood-serum or plasma with standard saline solutions of epinephrin, thereby ignoring the possible influence on the test tissues of the blood itself—effects which in every case are significant.^{13, 16, 15}

14. Hoskins: Jour. Pharm. and Exper. Therap., 1911, iii, 93.

15. Stewart: Jour. Exper. Med., 1911, xiv, 377. Kahn: München. med. Wehnschr., 1912, No. 13.

In Table 1 is summarized the results of our determinations of the epinephrin content of the "adrenal" blood. The proportions varied from approximately 1:2,000,000 to 1:8,000,000, with an average of 1:4,200,000. Figure 1 shows the tracings from which the estimation in case of Dog "B" was made. Our results as they stand are in satisfactory agreement with those of previous investigators. In common with those results, however, they involve two sources of experimental error. The blood was obtained under abnormal pressure conditions, and was necessarily collected during strong sensory stimulation incident to visceral exposure and operative trauma. The effects of abnormal pressure conditions are problematic; but strong sensory stimulation has been shown to result in excessive epinephrin secretion.³ It is altogether likely, therefore, that the estimated epinephrin content of the adrenal blood is higher than obtains under normal conditions.

Determinations of the rate of blood flow in the adrenal veins apparently have not been made.¹⁶ In Table 1 is included the rate at which the blood was collected in our experiments. It averaged 12.2 c.c. per minute. This rate probably only roughly approximates that under normal conditions. We found an average output of epinephrin of approximately 2.5 c.c. 1:1,000,000 solution per minute, or 0.25 c.c. per kilo per minute. O'Connor,¹³ using the same method of collecting the blood, has found in the rabbit an average flow of approximately 0.5 c.c. per minute. The concentration of epinephrin averaged about 1:2,500,000. The epinephrin output, then, would be equivalent to about 0.2 c.c. 1:1,000,000 solution per minute.

An indirect method of determining the epinephrin output suggested itself, a method which would obviate the abnormal conditions previously mentioned. We had noted that a certain amount of adrenalin can be injected into a femoral vein without producing any effect on blood-pressure. This fact can be interpreted in two ways: either the normal output from the animal's own adrenals is below the threshold value necessary to affect pressure, or the vasomotor system is not sensitive to variations in the quantity of circulating epinephrin of the magnitude used. By direct experiment it was found that differing effects were produced by variations in the quantity injected, which were decidedly smaller than the amount required to produce an initial effect. Figure 2, for instance, shows the results of injecting varying quantities of 1:500,000 epinephrin solution into the femoral vein while recording carotid pressure. The dog was sensitive to variations of 0.1 c.c., whereas 0.4 c.c. was required to produce an initial effect. Such results indicate that the quantity of epinephrin normally circulating is not sufficient to affect the vasomotor system.

16. Burton-Opitz: Personal Communication. 1912.

It appeared, then, that a comparison of the amount of epinephrin necessarily injected while the adrenals were intact to raise to an effective value the epinephrin content of the circulating blood with the quantity necessary after occlusion of the adrenal vessels, would show more or less accurately the quantity produced by the glands themselves.

Proceeding on this assumption, we made the determinations summarized in Table 2. While carotid blood-pressure was being recorded on a slow extension kymograph, adrenalin solution was injected from a buret connected with a cannula in the femoral vein. Thus normal epinephrin discharge was simulated. The buret was graduated to tenths of a cubic centimeter. The rate of outflow was regulated by an ordinary glass stop-cock. Adrenalin in Ringer's solution of 1:100,000 to 1:500,000 was employed as the conditions of each case required. For the more sensitive animals, of course the higher dilution was used. The purpose was

TABLE 2.—AMOUNT OF EPINEPHRIN REQUIRED FOR MINIMAL EFFECT ON BLOOD-PRESSURE BEFORE AND AFTER REMOVAL OF ADRENALS

Dog	Weight Kilos	Minimal Quantity Required Before Removal of Glands		Minimal Quantity Required After Removal of Glands		Difference, Adrenal Output	
		Per Dog*	Per Kilo ¹	Per Dog*	Per Kilo*	Per Dog*	Per Kilo*
F	6	1.5	0.25	3	0.5	1.5	0.25
G	8	3	0.37	5	0.6	2	0.25
H	5.6	4	0.71	5.6	1.0	1.6	0.29
I	4.0	1.8	0.45	2.4	0.6	0.6	0.15
J	7.2	2.8	0.38	3.6	0.5	0.8	0.12
K	4.9	0.3	0.06	0.6	0.13	0.3	0.07
L	6.4	3	0.47	3	0.47	0†	0
M	10	3.5	0.35	3.5	0.35	0†	0
N	4.6	3.5	0.76	3.5	0.76	0†	0
Av.	6.3	2.6	0.42	3.4	0.55	0.75	0.13

*The figures in this column represent c.c. of 1:1,000,000 solution.

†"0"=less than 0.1, the limit of sensitiveness of test.

to use a solution sufficiently concentrated to avoid the injection of significant quantities of fluid and sufficiently dilute to permit ready control of the rate of epinephrin injection. For convenience, the solutions are all expressed in the table as 1:1,000,000. The solution was freshly prepared in each instance just before use. Injections were made at various rates at short intervals until the minimal quantity necessary to affect pressure was determined. With such dilutions as were used, there was no impairment of sensitiveness during the experiment. Usually the injections were continued for thirty seconds. The experimental animals were etherized carefully to avoid excitement, and the cannulas were inserted with the

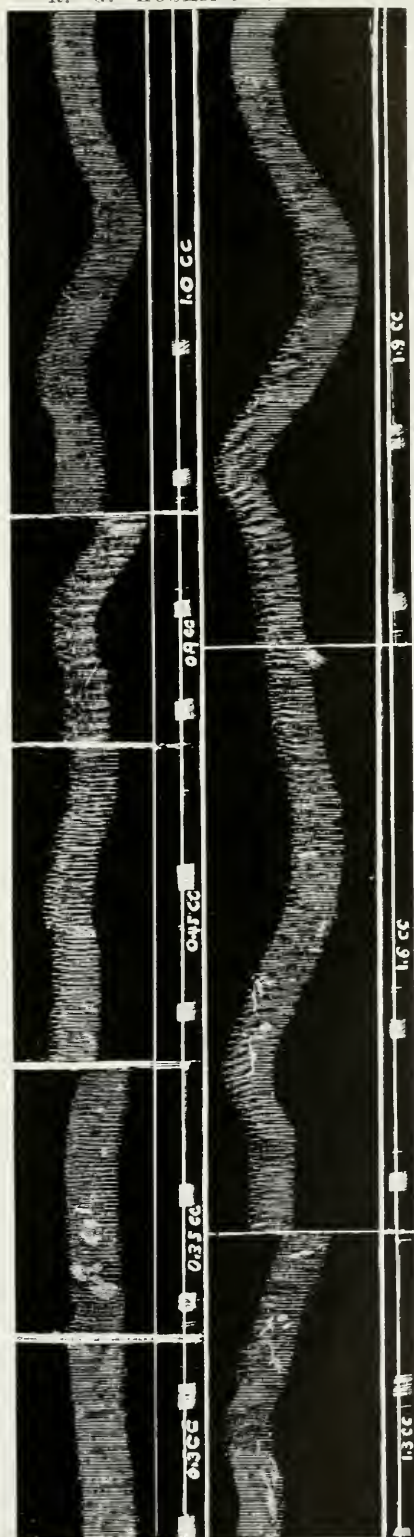


Fig. 2.—Effects of varying quantities of epinephrin on blood-pressure. Pressure from carotid artery of dog. Adrenalin 1:500,000 in Ringer's solution injected into femoral vein. Injections continued 30 seconds. Time, 30 seconds; blood-pressure, 120 mm. Quantities 0.3 cc. to 1.9 cc. Injections begun at first wide mark on signal line and discontinued at second.

least feasible trauma to avoid sensory stimulation, both of which influences have been shown to cause augmented epinephrin discharge.³ Uniform light anesthesia throughout the experiment was secured by causing the animal to breathe through a tracheal tube from a Wolff flask containing ether; by use of a short tube and small flask with large openings dyspnea due to rebreathing was avoided.

After the first determination was made the abdomen was opened by a median incision, and while the viscera were protected by warm towels an aneurysm needle carrying a double ligature was passed directly under each adrenal. Then the ligatures were brought up one to the mesial and one to the lateral side of each gland and securely tied. Thus each organ was completely isolated. Care was taken not to rupture the adrenal tissue, and thus to liberate any elaborated secretion which might be resorbed and vitiate the remainder of the experiment. The abdomen was closed, and after a few minutes delay to permit the immediate effect of the operation to pass off, a second series of injections was made and the minimal quantity required to affect pressure again determined.

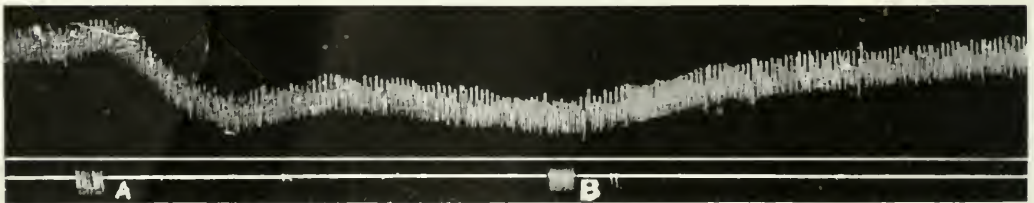


Fig. 3.—Record showing sustained vascular hypotension due to epinephrin. From a-b 0.8 c.c. 1:200,000 adrenalin in Ringer's solution (1 minute). Time, 30 seconds; pressure, 110 mm.

From Table 2 it appears that to affect pressure in the intact animal 0.12 c.c. per kilo of 1:1,000,000 epinephrin solution was required; after occlusion of the adrenal vessels 0.05 c.c. was required. Under fairly normal conditions, then, the adrenal glands had been producing as a maximum approximately 0.13 c.c. 1:1,000,000 solution of epinephrin per kilo, per minute. These findings indicate that the direct determinations of Table 1 (0.25 c.c. per kilo, per minute) were, as supposed, too high. These latter findings are probably also high, in that no allowance was made for a possible impairment of sensitiveness of the vasomotor system from the shock incident to tying off the adrenals. Support for this hypothesis is found in the fact that as greater facility in performing the operation was acquired, the difference in quantity of epinephrin required to affect pressure became continuously smaller. The later experiments of the series indicate a very minute output.

The data of Table 2 answer the question as to the rate of injection necessary to affect the blood-pressure of an epinephrectomized animal. An average of 0.55 c.c. 1:1,000,000 adrenalin per kilo per minute was required. Both Tables 1 and 2 indicate that epinephrin is not secreted in quantity sufficient to produce such effect. Table 1 shows a production of 0.25 c.c. and Table 2, 0.13 c.c. per kilo per minute. The very fact, however, that epinephrin can be injected into the femoral vein of an intact animal without affecting pressure while the animal reacts differentially to variations of less magnitude than the quantity first injected, seems to obviate any real necessity for answering the question. The data of Table 2 alone justify a positive conclusion that the adrenals do not ordinarily produce sufficient epinephrin to stimulate the sympathetic system.

The term *affect* rather than *raise* pressure has up to this point been used advisedly. Early in the researches it appeared that epinephrin is not, as ordinarily assumed, primarily a *pressor* agent. The primary effect of epinephrin administered in doses gradually transcending ordinary physiologic limits is *depression*. Figures 2 and 3 show the characteristic effects of minimal quantities of adrenalin. The first effect to appear is a brief, inconsequential rise followed by a subnormal pressure and a gradual return to normal while the injection continues (not shown in tracings reproduced). If the dose is slightly larger the subnormal pressure persists until the adrenalin is discontinued. (See Fig. 3.) If the dose is slightly further increased a pressor effect appears that may exactly cancel the depressor effect and leave the pressure after the initial fluctuation at normal level. Finally, with a dose again increased a sustained hypertension may be obtained. Thus, in one typical instance in which the point was specifically under investigation, although the characteristic primary effect appeared with the injection of 3 c.c. of 1:1,000,000 solution of adrenalin per minute, it was not until 17 c.c. was used that a minimal sustained rise occurred. The depressor effect of small quantities of adrenal extract has been noted from time to time by previous investigators, but it has been ascribed to general "depressants" that occur in tissue extracts.¹ Such an explanation, however, cannot apply to the effects of a pure isolated epinephrin, such as was used in these experiments.

As a preliminary note, mention may be made that in a series of experiments now under way but not yet completed, considerable evidence has been accumulated which indicates that intestinal peristalsis is brought to a stand-still by quantities of epinephrin inadequate to exert a pressor influence. These results, so far as they go, seem to indicate conclusively that adrenal secretion cannot be a direct factor in the maintenance of blood-pressure. An organism obviously could not make use of a mechanism which, to be effective in other regards, would stop peristalsis.

SUMMARY

1. Determinations by the rabbit intestine method indicate a difference in epinephrin content of the blood of dogs from the adrenal region of the vena cava, and that from the femoral vein of less than 1:100,000,000. This roughly indicates an epinephrin concentration in arterial blood of less than 1:200,000,000.

2. Similar determinations indicate an epinephrin content of blood from the lumbo-adrenal veins of 1:1,000,000 to 1:8,000,000, and an output of 0.25 c.c. 1:1,000,000 solution per kilo per minute. This value is probably higher than obtains under normal conditions on account of the sensory stimulation necessarily involved in collecting the blood.

3. Comparison of the amount of epinephrin required to affect blood-pressure with the adrenals intact with the quantity required after occlusion of the adrenal circulation indicates as a maximum an epinephrin secretion of 0.13 c.c. 1:1,000,000 solution per kilo per minute.— This value is also probably too high.

4. The amount of epinephrin necessary to affect blood-pressure is, on an average, approximately 0.42 c.c. 1:1,000,000 solution per kilo per minute in the intact animal, and 0.55 c.c. after removing the adrenal glands.

5. The characteristic primary effect of epinephrin administered intravenously is lowering of blood-pressure.

6. The quantity required to cause minimal hypertension is several times this quantity, or at least ten to twenty times the amount secreted by the adrenal glands.

7. Incomplete data indicate that peristalsis is depressed by quantities of epinephrin inadequate to raise blood-pressure.

8. Adrenal secretion is not, therefore, a direct factor in the maintenance of the tone of the vasomotor system.

9. It is probable, then, that other activities controlled by the sympathetic nervous system are not directly dependent on adrenal activity.

DISCUSSION

Realizing the unfortunate profusion of speculative literature on internal secretion, it is with some hesitation that we venture to discuss further the functions of the adrenals. Attention may be called, however, to certain data that seem in this connection especially significant.

Addison's and Brown-Séquard's early work prove conclusively that the glands do in some way promote the nutrition of the muscular tissues. Biedl's later work, however, makes it appear probable that this function is mediated by the cortical portion of the gland.¹ Data now available scarcely permit any deductions as to how this function is brought about.

Particularly significant, also, seems Elliott's² observation that plain muscle deprived of its sympathetic innervation acquires an increased irritability to epinephrin. This fact strongly suggests that the chromaffin tissue has a function of compensating for injury of sympathetic fibers. Thus, after sympathetic impulses fail, their place is taken by epinephrin stimulation of the nerve-endings.

Recent researches on adrenal control carried on at the Harvard Medical School³ in connection with such data as this paper affords, seem to indicate that chromaffin secretion is largely a reserve for times of special stress. Falta and Priestly¹⁷ have recently shown that the injection of large doses of epinephrin leads to an unusual distribution of the blood in the body. If the organs of an animal under the influence of this substance are quickly tied off an excess of blood is found in the lungs, brain, liver and kidneys, while the skin, spleen, mucous membranes and muscles are pale. That epinephrin strongly inhibits the alimentary canal and stimulates the heart is well known. During muscular activity there is an increased blood-flow in the particular muscles involved, brought about by local vasodilator mechanisms. If these local mechanisms be efficient to overcome the general constricting effect of circulating epinephrin on the blood-vessels of the muscles, as they obviously must be, there would seem to be provided an arrangement to bring about an adaptive distribution of the blood favorable to extreme muscular effort. Thus, structures not involved would remain quiescent with a restricted blood-supply while the *active* muscles, the central nervous system and the eliminative organs would be extensively supplied. Also a reserve food-supply, the glycogen of the liver, would be freely available to prevent the hypoglycemia that would otherwise quickly ensue.

The Harvard researches,³ in connection with Crile's¹⁸ principle of "phylogenetic association," explain how this adaptive mechanism may be brought into play. During the racial history, anger, fear, or pain have commonly resulted in combat or flight, either of which makes special demands on the muscular system. Excessive activity in turn leads to a condition of partial asphyxia. This condition, as well as the antecedent emotion or pain, causes an augmented epinephrin discharge, which in turn brings about the reactions previously mentioned. The hypothesis derives additional support from the fact observed by Cannon, Shohl and Wright¹⁹ that fear or anger in a quiescent animal actually does cause a condition of hyperglycemia. Macleod,²⁰ Edie, Moor and Roaf²¹ and others have noted a similar reaction to asphyxia.

17. Falta and Priestly: Berl. klin. Wchnschr., 1911, No. 47.

18. Crile: Boston Med. and Surg. Jour., 1910, cxliii, 893.

19. Cannon, Shohl and Wright: Am. Jour. Physiol., 1911, xxix, 280.

20. Macleod: Am. Jour. Physiol., 1909, xxiii, 302.

21. Edie, Moore and Roaf: Biochem. Jour., 1911, v, 325.

Finally, there is considerable evidence that the adrenals have important interrelations with other organs of internal secretion.²² Just what these relations specifically are, however, cannot yet be stated.

The data of this paper justify further emphasis of a principle mentioned in a previous communication.⁴ Studies directed toward the elucidation of the physiology of the adrenal glands must be *quantitative*. That the effects of epinephrin injection may vary qualitatively as well as quantitatively according to the amount used, is definitely proved. The actual effect in any organ is the algebraic sum of the effects on the component tissues — tissues which may have varying thresholds of irritability and may be affected synergetically, or, as in case of the intestine,⁴ antagonistically. The total effect may vary diametrically, depending on the amount used. Ignoring this fundamental principle of pharmacodynamics has led to many unjustified conclusions regarding adrenal functions. In any case, before any deductions regarding ordinary adrenal physiology can be made from the effects of epinephrin injections, it must be shown that the quantities used are within physiologic limits.

22. For a review of the literature see Hoskins, *Am. Jour. Med. Sc.*, 1911, cxli, (March and April).

THE DIAGNOSTIC WORTH OF THE GLYCYLTRYPTOPHAN AND THE TRYPTOPHAN TESTS IN DISEASES OF THE STOMACH *

A REPORT OF 1,175 CASES STUDIED BY A UNIFORM METHOD

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The surgeon and the pathologist have shown that when cancer of the stomach is diagnosed early that affection is as amenable to treatment as is cancer in other parts of the gastro-intestinal tract. At present, it would seem that early diagnosis rests largely on microscopic examination of sections of extirpated tissue. Inasmuch as prognosis is directly dependent on the process at diagnosis, it would appear desirable to elaborate certain diagnostic procedures that might anticipate laparotomy findings.

Recently the physiologic chemist has undertaken the investigation of biologic problems bearing on clinical medicine. Various workers, notably Müller,¹ Fischer,² and Abderhalden³ have reported that malignant neoplasms contain certain peptidolytic enzymes. This discovery appeared to have clinical value when Neubauer and Fischer⁴ announced that simple peptides, particularly the dipeptid, glycyltryptophan, were hydrolyzed by cancerous ferments. In the case of glycyltryptophan, the amino-acid, tryptophan, which is liberated by this cleavage, can be recognized readily in acid solution by the rose-pink color occurring on the addition of bromin. This reaction forms the basis of the "glycyltryptophan test" for cancer of the stomach, advanced by Neubauer and Fischer.

Clinicians generally have disagreed widely on the actual value of the test. The reaction's sponsors, together with Lyle and Kober⁵ and Weinstein⁶ early reported enthusiastically on the procedure. Later

*From the Laboratory of Gastro-Enterology, St. Mary's Hospital, Mayo clinic.

*Manuscript submitted for publication June 19, 1912.

*Read before the American Gastro-Enterologic Society, Atlantic City, June 3-4, 1912.

1. Müller: *Ztschr. f. klin. Med.*, 1889, xvi, 496.

2. Fischer: *Deutsch. Arch. f. klin. Med.*, 1902, lxxii, 415.

3. Abderhalden: *Ztschr. f. physiol. Chem.*, 1909, lxii, 136.

4. Neubauer and Fischer: *Deutsch. Arch. f. klin. Med.*, 1909, xciii, 499.

5. Lyle and Kober: *New York Med. Jour.*, 1910, xci, 1151.

6. Weinstein: *Jour. Am. Med. Assn.*, 1910, lv, 1085.

observers, especially Warfield,⁷ Oppenheim,⁸ Kohlenberger⁹ and, most recently, Sanford and Rosenbloom,¹⁰ declare that the test is of dubious value. They admit that while certain cases of cancer of the stomach undoubtedly give the reaction, many non-malignant gastric disturbances give similar tests. Factors claimed to influence the reliability of the reaction are swallowed saliva, bacteria, bile or blood in the gastric extracts, low or absent free hydrochloric acid and regurgitated duodenal contents.

In October, 1911, Weinstein¹¹ announced that he had improved on the Neubauer and Fischer test. He stated that in extracts from cases of carcinoma ventriculi there exist free amino-acids, notably tryptophan, and that the latter can be tested for directly with bromin. This procedure appeared to render unnecessary the addition of glycytryptophan to such gastric contents, with search for its cleavage products subsequently. This so-called "tryptophan test" was claimed as a reaction pathognomonic of cancer of the stomach. Weinstein did not, however, go so far as to state just how early in the progress of the disease this test could be regarded as pathognomonic. Certainly, in the clinical cases which he briefly quoted, when the tryptophan test was positive, other evidences of cancer were not lacking. Recently Hall and Williamson¹² and Sanford and Rosenbloom¹⁰ have recorded observations which appear to indicate that Weinstein's test has even less value than, in their experience, had the glycytryptophan test.

The great difference of opinion regarding the practical worth of the two tests mentioned led us to make the observations herewith submitted.

AUTHOR'S STUDY

From October 1, 1911 to May 15, 1912, the Ewald test breakfast was administered to 1,626 different individuals at St. Mary's Hospital (Mayo Clinic). On the gastric extracts from more than 1,400 of these patients, glycytryptophan and tryptophan tests were made. On 1,175 different individuals, the gastric extracts were tested according to the modification of the glycytryptophan and the tryptophan tests recently

7. Warfield: Bull. Johns Hopkins Hosp., May, 1911, 150.

8. Oppenheim: Deutsch. Arch. f. klin. Med., 1910-11, ci, 293.

9. Kohlenberger: Deutsch. Arch. f. klin. Med., 1910, xcix, 148.

10. Sanford and Rosenbloom: THE ARCH. INT. MED., 1912, ix, 445.

11. Weinstein: Jour. Am. Med. Assn., 1911, lvii, 1420.

12. Hall and Williamson: Lancet, London, 1911, clxxi, 731.

suggested by me.¹³ This modification appears to have the advantages of requiring less of the test ingredients than the Neubauer and Fischer method, of being a controlled procedure, and one in which the end-reaction may be easily determined. It is the purpose of this communication to report our experience with the cases tested by this uniform method.

Certain precautions taken in the manipulation of the reaction might be mentioned briefly. All glassware was boiled in distilled water and dried before using. The solution of glycytryptophan employed was obtained, in bulk and unopened, direct from the makers. To guard against its tendency to crystallize out, in cold solution, the preparation was kept in a water-bath at 37° C. until used. All gastric extracts were carefully filtered before testing, and the tests were set up within two hours, at the outside, from the time the contents were taken from the

13. The test is set up as follows:

1. Test-tubes of 10 c.c. capacity are employed. These should be carefully cleaned with boiling water and dried inside. They are numerically marked for identification with a wax pencil. Into each test-tube is carefully measured, by means of a sterile graduated pipet, 0.5 c.c. of the glycytryptophan solution. Five c.c. of the recently secured filtered gastric extract are then measured by a clean, graduated pipet and poured into the correspondingly numbered test-tubes to which glycytryptophan solution has been already added. Two control tubes are used. In one is placed 0.5 c.c. of glycytryptophan solution and 5 c.c. of normal salt solution, and into the other is placed 5 c.c. of normal salt solution, without added glycytryptophan solution. In the entire series, each tube next receives 0.5 c.c. of toluol (Toluene, Merck). The contents of the tubes are then mixed by inverting several times. The tubes are next placed in a water-bath (an incubator may be used) at 37° C. for twenty-four hours.

2. At the expiration of the incubation period, the test-tubes are removed from the water-bath. Clean test-tubes of 10 c.c. capacity and numbered to correspond with the gastric extracts tested, as well as the controls, are set in racks. Into each of these tubes is measured by means of a graduated pipet, 2 c.c. of the glycytryptophan-gastric-extract mixture lying below the toluol in the recently incubated tubes. To each tube are then added three drops of a 3 per cent. glacial acetic acid in distilled water solution. The tubes are well shaken. Bromin vapor is allowed to flow into each tube until it appears amber yellow above the contained fluid. The tubes are again shaken. Examination by daylight (preferred) or by white, artificial light is now made for evidences of the characteristic rose-pink reaction between the amino-acid (tryptophan) and the bromin.

Tryptophan Test: As suggested by Weinstein, this is made, as routine, on the fresh gastric extracts, inasmuch as, occasionally, swallowed saliva, amino-acids, regurgitated duodenal contents and the like may give the bromin vapor reaction, before incubation or without the addition of a dipeptid such as glycytryptophan. Five c.c. of each fresh, filtered gastric extract are poured into test-tubes of 10 c.c. capacity, acidulated with the 3 per cent. acetic acid solution and treated with bromin vapor as above. If no characteristic rose-pink color results, the tubes are incubated with the corresponding specimens that have been mixed with glycytryptophan solution. For accurate work, it has seemed best to us to cover these "tryptophan test" contents with a layer of toluol. At the end of twelve, twenty-four and forty-eight hours, note is made of changes in color, and these results are compared with those obtained with the preparations in the first series. *Jour. Am. Med. Assn.*, 1912, lvii, 1008.

patients. In testing for tryptophan, before or after incubation, bromin vapor was preferred over bromin water. It is more readily controlled quantitatively and permits of better color determination. All end reactions were read by daylight.

TYPICAL REACTIONS

When bromin vapor is used for the detection of amino-acid (tryptophan), its presence is indicated, even in small amounts, by lilac-violet to rose-pink shades. The color is usually a lively one, and appears quickly. Admixtures of much blood and bile produce, respectively, dirty, brownish-yellow and muddy-green to drab. In such, gradations in shade are impossible. High organic acidity often gives rich purple or magenta hues. When the color change is opalescent, with bluish or delicate lilac cast, the results may be classed safely as negative.

RESULTS

The gross results of our observations are as follows: Of 1.175 gastric extracts from individuals with gastric symptoms, clinically, 110, or 9.36 per cent., were glycytryptophan positive. In the same cases, 24, or 2.04 per cent., were tryptophan positive, either before or after incubation. Tables 1 and 2 show, respectively, the number of positives with each test, associated with different diseases. Tables 3 and 4 respectively consider the clinical and laboratory data.

TABLE 1.—SUMMARY OF CASES GIVING POSITIVE GLYCYLTRYPTOPHAN TEST

Diagnosis	No. of Cases	Diagnosis	No. of Cases
Carcinoma ventriculi.....	31	Achylia gastrica.....	6
Ulcus ventriculi.....	9	Appendicitis.....	8
Carcinoma of the liver.....	3	Primary anemia.....	3
Ulcer of duodenum.....	3	Syphilis—stomach.....	1
Non-malignant pyloric obstruction.	1	Various (gastritis, gastric neurosis,	
Cholecystitis.....	11	chronic diarrhea, epilepsy) ..	10
Gall-stones.....	6		
Hypochlorhydria.....	7	Total.....	110
Achlorhydria.....	11		

TABLE 2.—SUMMARY OF CASES GIVING POSITIVE TRYPTOPHAN TEST

Diagnosis	No. of Cases	Diagnosis	No. of Cases
Carcinoma ventriculi.....	7	Appendix lesions.....	1
Ulcus ventriculi.....	3	Various (neuroses, achlorhydria,	
Ulcer duodenum.....	3	arteriosclerosis).....	6
Carcinoma of the liver.....	1		
Gall-stones.....	3	Total.....	24

It will be noted that one of the valuable features of the tables is the fact that the majority of the cases exhibiting positive reactions were treated surgically; hence, the conclusions derived from consideration of the figures returned have a fairly definite pathologic basis.

TABLE 3.—CLINICAL AND LABORATORY DATA OF THE CASES RETURNING POSITIVE GLYCYLTRYPTOPHAN TEST

Number and Name	Diagnosis	Total Acidity	Free HCl.	Blood	Bile	Lactic Acid	Degree of Reaction*
61563—Leslie	Gall bladder infect.	46	36	+	0	0	+
9532—Graham	Anemia (post. mort.)	0	0	+	0	0	+
61743—Belanger	Duodenal ulcer—opr.	86	80	0	++	0	+
61000—Smith	Gall bladder	46	40	0	0	0	+
61795—Hillis	Gastritis chr.	14	6	+	0	0	+
61857—Kise	Carcinoma stom.—opr.	0	0	++	0	0	++
61802—Fuller	Gastritis; chr. append.	4	0	+	+	?	+
38406—Pew	Gall bladder infect.	6	0	0	0	0	++
53228—Reede	Gastric neurosis	18	18	+	0	0	++
61852—Koss	Carcinoma stomach	4	0	+	0	0	++
61910—Graybill	Carcinoma stomach—opr. ..	0	0	++	0	++	+
61812—Letoman	Epilepsy	10	10	+	+	0	++
61940—Beck	Gastritis—chr.	24	24	0	0	0	+
61862—Huseby	Gastric neurosis	40	30	0	+++	0	+
61974—Longtime	Gastritis—alcoholic	0	0	+	+	+	++++
62100—Schaffer	Carcinoma stomach—opr. ...	20	0	+	0	+	+
62171—Plan	Carcinoma stom. opr.	48	0	+	0	++	+
62086—Haley	Gastritis—chr.	10	0	0	++	0	+
62089—Moldenhauer ..	Gastric ulcer	40	40	0	+	0	+
62219—Biehl	Carcinoma stom.—opr.	24	12	+	0	0	+
62154—Ahlborn	Carcinoma stom. opr.	8	0	0	+	0	++
62233—Flick	Carcinoma liver—expl.	24	24	+	+	0	++
62260—Chapman	Pyloric obstr. non-malignant.	40	32	++	+	0	+
62399—Baum	Carcinoma stom.—opr.	0	0	+	0	0	+
53032—Kopplow	Duodenal ulcer—opr.	50	50	Tr.	+	0	+
62562—Dunn	Carcino. Gall Bl. opr.	6	0	+	+	0	+
62665—Warner	Gastric ulcer	28	28	Tr.	+	0	++
37124—Nelson	Carcin. stom. recur.	8	0	0	+	0	+
61072—Zielsdorf	Gall stones—opr.	56	40	0	Tr.	0	+
62876—Johnson	Cholecystitis	10	0	Tr.	++	0	+++
62912—Erickson	Chr. Ap. opr.	22	18	Tr.	+	0	+
62971—Maxwell	Chr. Ap. opr.	22	0	0	+	0	+
62977—Hanson	Ulcer stomach	48	40	0	0	0	+
63026—Brooks	Chr. Appendicitis	32	32	+	+	0	+
63051—Marian	Neg. Stom. Ap.	36	32	0	+	0	+
63093—Taylor	Chr. Diarrh. stom. neg.	4	0	0	0	0	+
63129—Erickson	Stom. ulcer and G. B. opr. ..	32	30	+	0	0	0
63130—Weech	Chr. App. opr.	0	0	0	0	0	+
62699—Wright	Cholangitis	0	0	Tr.	0	0	+
63030—Gladens	Carcinoma stomach	8	0	0	0	0	+
63241—Berend	Carcinoma stomach opr.	56	18	+	0	0	+
63292—Glaesner	Gastric ulcer	46	46	+	+	0	+
63197—Smith	Multiple sclerosis	20	6	0	+	0	+
63335—Given	Duod. ulcer; cholecystitis ..	48	40	0	+	0	+
52034—Rice	Recurrent Ca. stomach.	10	0	+	+	0	+
62876—Johnston	Syph. stom.	0	0	0	0	0	+
63506—Bragen	Gastritis	38	22	0	+	0	+
63547—Hanson	Resect. stom. ca.	0	0	+	0	?	+
63562—Arms	Arteriosclerosis	0	0	0	0	0	+
63600—Lutke	Appendicitis—neg.	44	40	0	+	0	+
63616—Rarity	Appendix and G. B. opr.	12	0	0	+	0	+
63653—Allen	Ulcer stom. opr.	32	28	Tr.	+	0	+
63636—Carlson	Gall stones—opr.	22	0	0	0	0	+
63778—Thompson	Carc. stom.	14	0	+	+	+	+
36634—McEvan	Ulcer stom.	40	30	+	0	0	+

TABLE 3.—CLINICAL AND LABORATORY DATA OF THE CASES RETURNING POSITIVE GLYCYLTRYPTOPHAN TEST (Continued)

Number and Name	Diagnosis	Total Acidity	Free HCl	Blood	Bile	Lactic Acid	Degree of Reaction*
63883—Bond	Gall stones—opr.	6	6	0	0	0	+
64057—Atol	Hypochlorhydria	8	0	+	++	0	+
64039—Olson	Achlorhydria	0	0	0	0	0	+
61915—Even	Hypochlorhydria	4	4	0	0	0	+
64270—Gregg	Ulcer stom. opr.	50	46	+	0	0	+
64330—Schuler	Carc. stomach	14	0	+	0	+	+
64360—Berg	Neurosis	54	50	0	+	0	+
64482—Smeath	Carc. stom. resect	8	0	+	0	0	+
64455—Norres	Hypochlorhydria	4	0	+	0	0	+
64281—Seedhug	Achylia gastr.	0	0	+	0	0	+
34078—Johnston	Neuroses	42	40	0	0	0	+
64877—Hutchinson	Cholecystitis	4	0	0	0	0	+
65179—Otter	Appendicitis	36	26	0	Tr.	0	+
65229—Arnold	Ca. stom. and liver	0	0	+	0	0	+
65293—Aklund	Achlorhydria	8	0	0	+	0	+
65337—Verner	Cholecystitis, appendix	16	0	0	Tr.	0	+
37889—Gehrke	Appendicitis opr.	12	12	Tr.	0	0	+
65692—Rule	Gall stones and appendix opr.	38	14	24	+	0	+
22528—Shaffer	Duod. ulc. opr.	8	0	0	0	0	+
65703—Gaskill	Degen. gast. ulc.	8	0	0	0	0	+
65835—Ellwell	Gen. carc. prim. stom.	0	0	0	0	0	+
65901—Hovelsrud	Carc. stom.	6	0	+	0	0	+
5231—Graft	Achlorhydria	8	0	0	+	0	+
65953—Eaton	Achlorhydria	12	0	0	+	0	+
66017—Richie	Carc. stom.	30	0	+	0	0	+
66108—Graham	Gall stones opr.	8	0	0	+	0	+
66225—Bryant	Pernicious anemia	40	0	+	0	0	+
64942—Hester	Second. anemia	10	0	0	0	0	+
66314—Spellman	Cholecystitis	30	30	0	+	0	+
66333—Wickman	Gall stones opr.	10	0	+	0	0	+
66409—Bronson	Achlorhydria	20	0	+	0	0	+
66462—Bram	Gastric ulcer	26	26	+	0	0	+
56586—Carr	Cancer stom. recur.	48	48	0	0	0	+
66466—Stevenis	Achlorhydria	48	0	0	0	0	+
63547—Harrison	Cancer stom. resect.	12	0	Tr.	0	0	+
66511—Lane	Achlorhydria	4	0	0	0	0	+
66583—Miller	Cholecystitis	50	50	0	0	0	+
66644—Andrew	Carc. stom.	12	0	0	0	0	+
66787—Leutke	Achlorhydria	20	0	Tr.	0	0	+
66904—Boe	Achlorhydria	34	0	Tr.	0	0	+
66855—Fozenden	Carc. stom. opr.	26	26	+	0	0	+
66864—Hennessy	Hypochlorhydria	12	12	+	0	0	+
67000—Stanley	Deg. gast. ulc.	26	26	+	0	0	+
45833—Thompson	Hypochlorhydria	8	8	+	0	0	+
67110—McKay	Cancer stomach	20	0	+	0	+	+
67112—Rasmussen	Gastric neurosis	38	24	0	0	0	+
67077—Snyder	Carc. liver and spleen	80	80	0	0	0	+
67206—Allen	Carc. stom.	14	0	0	+	0	+
67295—VanHook	Hypochlorhydria	18	8	Tr.	+	0	+
67368—Tucker	Carc. stom.	50	50	+	0	0	+
67690—O'Rourke	Pernicious anemia	4	0	0	+	0	+
67928—Hayes	Ca. stom. P. A. (?)	14	0	+	0	0	+
67562—Wessling	Gall stone opr.	12	0	0	0	0	+
67537—Owmen	Expl. cancer stom.	20	0	0	0	0	+
67644—Haggen	Achlorhydria	4	0	0	0	0	+

*Degree of Reaction: Lilac=+; Rose-pink=++; Rose-purple=+++.

Cancer: The total number of proven cases of cancer of the stomach, primary or secondary, in this series is eighty-seven. Of this number, thirty-one, or 35.6 per cent., gave positive glycytryptophan tests, while seven, or 8.04 per cent., were tryptophan positive. Of the thirty-one cases of cancer in which the glycytryptophan test was positive, the tryptophan test was positive but four times. In three cases in which the tryptophan test was positive, the glycytryptophan test was negative.

TABLE 4.—CLINICAL AND LABORATORY DATA OF THE CASES RETURNING POSITIVE TRYPTOPHAN TEST

Number and Name	Diagnosis	Total Acidity	Free HCl	Blood	Bile	Lactic Acid	Degree of Reaction*
61508—Theen	Stom. neg	36	36	0	+	0	+
61496—Fitzsimmons ..	Duod. ulcer opr.	56	38	0	0	0	+
61567—Crane	Gastric ulcer	42	20	0	+	0	+
61552—Eldred	Carcinoma stom. inop.	38	18	+	0	+	+++
62233—Flick	Carcinoma liver and G. B. .	24	24	+	+	0	+++
62784—Drechsler	Gastric ulcer clin.	12	12	+	0	0	+
62876—Johnson	Achlorhydria and G. B.	10	0	+	+++	0	+
62865—Zenk	Appendix chronic	24	18	Tr.	+	0	+
63051—Marion	Gastric neurosis	36	32	0	+	0	+
63230—Gladens	Carcinoma stom. (mass) ...	8	0	0	0	0	+
63241—Burend	Gastric carcinoma, resect. .	58	18	+	0	0	+
63221—Quinn	Gall-stone empyema G. B. .	20	20	0	Tr.	0	+
63414—Hanson	Duodenal ulcer opr.	80	80	0	+	0	+
63408—Lynch	Carcinoma stom. opr.	66	60	0	0	0	+
63653—Allen	Gastric ulcer clin.	32	28	Tr.	0	0	+
63354—Kissman	Tabes—crises	4	0	+	0	0	+
63563—Arms	Arteriosclerosis Gen.	0	0	0	0	0	+
63536—Carlson	Gall stone opr.	22	0	0	0	0	+
64394—Davis	Duodenal ulcer opr.	66	60	0	0	0	+
64294—Thoet	Carcinoma stom. opr.	14	4	+	0	+	+
65693—Rule	Gall stones and append. opr.	38	14	+	0	0	+++
5231—Graf	Gastric ulcer degen. post opr.	8	0	0	+	0	+++
56586—Carr	Carcinoma stom. recur.	48	0	0	0	0	+
67112—Rasmussen ...	Gastric neurosis	38	24	0	+	0	+++

*Degree of Reaction: Lilac=+; Rose-pink=++; Rose-purple=+++.

Of nine gastric ulcers with fair evidence of carcinomatous degeneration (of the type described by MacCarty¹⁴), two, or 22.2 per cent., gave the glycytryptophan reaction. In these same cases there was no positive tryptophan test. If we combine the returns from these cases with those from the specimens of advanced carcinoma, we note that the glycytryptophan test is positive in 35.4 per cent. and the tryptophan in 7.28 per cent., or the glycytryptophan test is positive approximately five times as frequently as is the tryptophan test.

14. MacCarty: Surg., Gyn. and Obst., 1910, x, 449.

Gastric Ulcer: In none of thirty-five operated gastric ulcers (microscopically carcinoma-free) was the glycytryptophan test positive. The tryptophan reaction was obtained once.

Thirty-nine cases were clinically diagnosed as gastric ulcer. Three of these (7.4 per cent.) were glycytryptophan-positive, and two (5.2 per cent.) were tryptophan-positive.

Duodenal Ulcer: Operations were performed on seventy-eight patients with duodenal ulcers. Of this number, three (2.6 per cent.) gave glycytryptophan and tryptophan tests. They were not identical cases and the reactions were not always associated with low acidity.

Fifty-seven individuals had duodenal ulcer, clinically. One (1.7 per cent.) was glycytryptophan-positive. None gave the tryptophan test.

TABLE 5.—THE RELATION OF GLYCYLTRYPTOPHAN TEST TO ACIDITY

Group	No. of Posi- tives	No. of Nega- tives	Group	No. of Posi- tives	No. of Nega- tives
Extracts having no acid- ity	14	20	Extracts having de- creased T. A.	88	515
Extracts having no free HCl	52	31	Extracts having nor- mal T. A.	17	213
Extracts having dimin- ished HCl	15	214	Extracts having in- creased T. A.	5	337
Extracts having normal HCl	22	369	Totals	110	1,065
Extracts having increas- ed HCl	7	431	Extracts having lactic acid	11	33
Totals	110	1,065			

Other Gastric Conditions: It has been advanced by Weinstein, Warfield, and Sanford and Rosenbloom that positive glycytryptophan reactions are usually obtained in gastric extracts exhibiting achylia or low hydrochloric acid. These reactions are claimed to result from the presence of a peptid-splitting enzyme (Warfield) existing in saliva. Gies¹⁵ thinks that mouth-bacteria may be capable of splitting simple peptides under these conditions. In order to determine the results in our cases from the view point of acidity, we have compiled Tables 5 and 6. It will be seen that about 60 per cent. of the positive glycytryptophan tests were obtained from extracts showing no free hydrochloric acid, while in an additional 13.6 per cent., the free hydrochloric acid was low. In other words, nearly three-fourths of the positives occurred in gastric extracts showing diminished acidity. Table 5 also brings out the interesting fact that approximately 80 per cent. of the

15. Gies: Quoted by Weinstein, Jour. Am. Med. Assn., 1911, lvii, 1420.

glycyltryptophan reactions were returned by contents in which the total acidity was low.

The support which these figures apparently give to Warfield's saliva ferment-action on peptids is qualified when one considers the negative glycyltryptophan tests in Table 5. Fifty-one of these extracts showed no free hydrochloric acid. In 214 extracts the free hydrochloric content was diminished. The combination of these results demonstrates that about one-fourth (24.8 per cent.) of the negatives was associated with low free hydrochloric acid. It could scarcely be maintained that all these extracts were saliva-free. Table 3 shows that some of the extracts were from cancerous patients. Approximately one-half (48.3 per cent.) of the negative glycyltryptophan tests were on extracts with diminished total acidity.

TABLE 6.—THE RELATION OF TRYPTOPHAN TEST TO ACIDITY

Group	No. of Posi- tives	No. of Nega- tives	Group	No. of Posi- tives	No. of Nega- tives
Extracts having no acid- ity	1	33	Extracts having de- creased T. A.....	17	586
Extracts having no free HCl	6	77	Extracts having nor- mal T. A.....	2	228
Extracts having dimin- ished HCl	10	219	Extracts having in- creased T. A.....	5	337
Extracts having normal HCl	4	387	Totals	24	1,151
Extracts having increas- ed HCl	3	435	Extracts having lactic acid	2	42
Totals	24	1,151			

A consideration of the relation of the tryptophan test to acidity is of interest. Of the positives seven, or 28.9 per cent., of the contents contained no free hydrochloric acid. In seventeen (75 per cent.) of the positives the free hydrochloric acid was diminished or absent. This combined figure is practically identical with that returned by the glycyltryptophan positives, although the percentage of extracts containing no free acid is much lower. In the tryptophan positives it will be seen that 75 per cent. showed diminished total acidity as against 80 per cent. in the case of glycyltryptophan positives.

Studying the negative tryptophan reactions, we note that in 329 instances (28.6 per cent.) there was absent or diminished free acid, while in 586 cases (50.8 per cent.) the total acidity was low. These figures closely approximate those shown by the tabulations from the negative glycyltryptophan reactions.

It would appear that Weinstein's contention that his tryptophan test removes the consideration of contaminating saliva as a source of

error is not borne out by our study. Further, the presence of negative glycytryptophan reaction, in so large a percentage of extracts with low acidity, leads one to the opinion that the significance of the peptidase, said to exist in saliva, as a factor in hydrolyzing glycytryptophan added to gastric extracts, is quite questionable. This opinion is substantiated by work we have done on saliva, soon to be reported.

Organic Acid: Ten per cent. of the positive glycytryptophan tests were associated with the presence of lactic acid. With the exception of one, the cases were carcinoma. Thirty-three negative reactions (3.9 per cent.) were in contents containing lactic acid. Eight and one-third per cent. of the positive tryptophan tests were present in lactic-acid-containing extracts, while forty-two (3.6 per cent.) negative tryptophan contents contained lactic acid. It would seem that organic acids have little bearing on the relative variation of the two tests.

TABLE 7

(A) THE RELATION OF BILE TO GLYCYL-TRYPTOPHAN TEST				(B) THE RELATION OF BILE TO TRYPTOPHAN TEST			
Groups		Bile present	Bile absent	Groups		Bile present	Bile absent
Glycytryptophan	positive.	39	71	Tryptophan	positive.....	10	14
Glycytryptophan	negative	320	945	Tryptophan	negative.....	349	802
Totals		359	816	Totals		359	816

Of the entire number of gastric extracts (1,175) analyzed in this series, forty-four, or 3.7 per cent., contained lactic acid by the controlled Uffelmann test. Of the cases proved to be carcinoma ventriculi, lactic acid was present in twenty-five (28.7 per cent.). As we have shown in these cases, the glycytryptophan reaction was positive in thirty-one (35.6 per cent.) and the tryptophan test in seven (8.0± per cent.). The relatively low percentage of extracts containing lactic acid may be explained on the basis of early diagnosis, many cases being operated on before marked obstruction and retention had developed. Emerson¹⁶ states that in his series of cases of carcinoma ventriculi, lactic acid was present in approximately 90 per cent. From our experience, it would appear that the great majority of his cases were far advanced and exhibited marked retention. High mixed organic acidity frequently gives confusing Uffelmann reactions.

It has been held that the *chyle* in gastric extracts vitiates the glycytryptophan test, but need not be considered when making the tryptophan test. The presence of bile or evidences of tryptic digestion has been used as proof that duodenal contents have been mixed with gastric juice.

16. Emerson: "Clinical Diagnosis," 1906.

The significance of this supposition is shown by analysis of Table 7. The gastric extracts were judged macroscopically as to the presence of bile and were also tested by means of the Pettinkofer or the fuming nitric acid reaction. It will be seen (a) that of 110 positive glycytryptophan reactions, thirty-nine (35.4 per cent.) contained bile; of 1,065 negative reactions, 320 (20.4 per cent.) showed bile; of the twenty-four positive tryptophan tests (b), ten (41.6 per cent.) were in bile-containing extracts, while 349 (30.4 per cent.) negative tryptophan tests were bile-positive. These figures do not demonstrate that the tryptophan test is uninfluenced by bile in the extracts. It is worthy of note that a relatively high number of both glycytryptophan and tryptophan reactions are found in bile-containing chyme.

TABLE 8

(A) THE RELATION OF BLOOD TO GLYCYLTRYPTOPHAN TEST			(B) THE RELATION OF BLOOD TO TRYPTOPHAN TEST		
Groups	Bile present	Bile absent	Groups	Bile present	Bile absent
Glycytryptophan positive.	56	54	Tryptophan positive.....	10	14
Glycytryptophan negative	236	829	Tryptophan negative.....	282	869
Totals	292	883	Totals	292	883

The effect of blood, traumatic or "occult," in gastric extracts has at least two points worthy of consideration with regard to the glycytryptophan and tryptophan tests. Traumatic blood of itself gives a tan or definitely red cast to filtrates. A color reaction such as we are discussing is readily effected by such shades. The second point of note is the possibility of tryptophan resulting from split digestion products of the blood itself, particularly in those cases in which there is marked gastric retention with much flora. Table 8 furnishes interesting data on the above points. In fifty-six (50.9 per cent.) of the glycytryptophan positive extracts, blood, traumatic or altered, (benzidin test) was present. Of the glycytryptophan negative extracts, in 236 (22 per cent.) blood was demonstrated. Of the tryptophan positive extracts, ten (41.6 per cent.) contained blood. In 282 (24.6 per cent.) tryptophan negatives, blood was proved. These figures for both tests so closely approximate that it does not seem possible to state that advantage lies with either. The relatively high percentage of positives in extracts containing blood should, however, be borne in mind.

SUMMARY

The work submitted makes apparent the following:

1. In our series, more than one-third of the proved cases of cancer of the stomach gave positive glycytryptophan reactions; more than one-fourth were lactic-acid-positive and about one-thirteenth of the number

exhibited the tryptophan test. Diagnosis of malignant disease of the stomach was in each case quite possible, independent of the above chemical reactions. As a test associated with cancer of the stomach, it will be seen that in our series the glycytryptophan reaction proved more consistent than tests for common organic or existing free amino-acid (tryptophan).

2. While gastric conditions other than cancer exhibit positive glycytryptophan reactions, in no single class of disease of the stomach is this test obtained so frequently as in cancer. This fact is of considerable significance chemically and, perhaps, etiologically. While cancer of the stomach can doubtless be diagnosticated clinically without the glycytryptophan test, one cannot state that the study of this and allied reactions will prove valueless.

3. Our work does not show that the tryptophan test is, as has been advanced, pathognomonic of cancer.

4. Low free hydrochloric or total acidity is frequently determined in gastric contents exhibiting positive glycytryptophan, lactic acid and tryptophan reactions. One cannot state positively that this diminished acidity is causative. Many cases of low acidity were negative to the above tests.

5. Approximately one-half of the positive glycytryptophan and tryptophan reactions were in gastric extracts containing bile and blood elements. Approximately one-fourth of the negative extracts contained blood and bile elements.

AN EXPERIMENTAL STUDY OF RACIAL DEGENERATION IN MAMMALS TREATED WITH ALCOHOL *

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It is recognized, by most observers who have studied the subject, that alcohol may play an important rôle in the causation of monstrosities and of structural defects predisposing to later disease. This view is based largely on observations on defective human beings, and the probability of its truth is sufficiently established to warrant further careful experimental analysis.

The quality of an offspring depends on two factors, the perfection of the germ cells from which it arises and the nature of the environment in which it develops. Diseased and weakened germ-cells give rise to a defective individual under all circumstances, while perfect germ-cells produce a perfect offspring *only* when the embryo develops in a normal or favorable environment. These facts may be readily demonstrated in lower vertebrates in which the development of the egg is outside the mother's body. The egg or spermatozoon in such cases may easily be chemically modified or injured before fertilization, and the embryo itself may be affected in various ways during its development by subjecting it to unusual surroundings, either physical or chemical. In other animals, such as mammals, in which the embryo develops internally, the proposition likewise holds true. In these animals, however, the problem is more difficult to completely analyze. The reactions of the parental body, the secondary conditions induced by the experimental treatment and other sources of error should be fully considered in determining whether an effect shown by the offspring is directly due to the applied stimulus or to secondary conditions. In the lower vertebrates it has been shown that given doses of certain substances induce definite developmental defects. The defects are directly due to the treatment. Is it possible by the addition of certain chemicals to the mammalian body to obtain similar definite changes in either the germ-cells or the developing embryo?

In the present paper I shall endeavor to show that alcohol does act directly on the germ-cells of mammals to a sufficient degree to render them incapable of producing normal offspring, and further, that similar treatment administered to the pregnant female may likewise act directly on the developing embryo so as to modify its resulting structure.

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First to appreciate fully the general status of the problem it is well to consider in a somewhat critical manner the literature pertaining to the actions of alcohol and other substances on the reproductive glands and developing embryos of man and lower animals.

DISCUSSION OF LITERATURE

There is an abundant literature relating to the effects of alcohol on the offspring, though little of it is scientifically reliable. I have attempted to select those cases which seem most trustworthy. Since we are more interested in the general problem of the effects of parental poisoning on the germ-cells and the embryo in mammals I have also collected the works relating to injurious substances other than alcohol. The observations and statistics on human beings in various countries are reliable only in so far as they may be substantiated and borne out by controlled experiments on lower animals. Yet in the light of animal experiments many of these human records become of surprising interest, although few if any of them may be accepted entirely as they stand.¹

EFFECT ON THE MALE GERM-CELLS

It is a well known and universally accepted fact that alcohol does cause changes and degeneration in many of the body tissues of man. The question naturally presents itself, How, then, can the reproductive tissues escape? Nieloux and Renault have shown that alcohol has a decided affinity for the reproductive glands. In the testicular tissues and the seminal fluid an amount of alcohol is soon present which almost equals that in the blood of a person having recently taken alcohol. The proportion of alcohol in the testis as compared with that in the blood was as 2 to 3, and in the ovary of female mammals as 3 to 5. The genital glands show as great an affinity for this substance as does the nervous system. From these observations it must necessarily follow that alcohol may act on the ripe spermatozoon shortly before the time when it fertilizes the egg, and since an affected spermatozoon gives rise to a defective individual, we have a probable explanation for many of the recorded defects attributed to drunkenness at the time of conception. A male, even for the first time, in a state of acute intoxication, is probably more apt to beget an abnormal offspring by fertilizing an egg at this particular period than is a non-intoxicated male although a frequent user of alcohol. The experimental data on the sensitiveness of the spermatozoon and the observations on the presence of alcohol in the seminal fluid warrant this statement.

1. Most of the literature is devoted to considerations of disease and insanity statistics and the family records of degenerates. The data are often collected in a careless fashion so that the *actual observations* are not always scientifically correct though the records are carefully and fully computed.

Lippich claims to have observed ninety-seven children resulting from such conceptions. Only fourteen of these were without noticeable defects. Eighty-three of them showed various abnormal conditions, twenty-eight were scrofulous,² three had "weak lungs," three showed different atrophic conditions, one watery brain, four were feeble-minded, etc. Others have made similar observations. Sullivan reported seven cases of drunkenness during conception which are fairly authentic. Six of the offspring died in convulsions after a few months, and the seventh was still-born.

Thus one finds proof by Nicloux and Renault that alcohol does reach the reproductive glands and, therefore, may affect the egg or sperm-cell, and observations seem to indicate that this effect expresses itself in the condition of the resulting offspring. Experiments on lower animals support the probability. When the perfectly normal spermatozoa of frogs are treated with α -ray or radium, Bardeen and O. Hertwig have shown that normal eggs fertilized by such spermatozoa all develop abnormally. Todde found that the offspring from alcoholized roosters were not quite normal and that the roosters did not succeed as well as normally in fertilizing eggs.

Combemale, 1888, was the first to experiment on the influence of alcohol on the mammalian offspring. He treated a dog for eight months with absinthe (11 gr. per day per kilo of animal weight) and paired this alcoholized dog with a normal bitch. Twelve young resulted; two were born dead, three died within fourteen days and the others died between thirty-two and sixty-seven days of intestinal catarrh, tuberculosis, etc. In a second experiment both parents were mated while normal, then the female was made drunk for twenty-three days (2.75 to 5 gr. absinthe of 72 per cent. per day per kilo). Of six young three were still-born, two had normal bodies though of weak intelligence, while one moved slowly and was very stupid. The last individual, a female, was later paired with a normal intelligent non-alcoholic dog. She gave only three young; one was deformed, club-footed with abnormal³ teeth, the second had a patent ductus arteriosus and died after fourteen days, while the third was poorly muscled in the hinder parts and died a few hours after birth. Thus the effects in the second generation are as pronounced as in the first although neither parent had themselves received any alcohol. The only criticism against Combemale's experiments is that an insufficient number of animals was used. Dogs often give defective pups and these may have been from poor stock, though such an interpretation is really not probable, and his results are supported by subsequent workers.

2. Imbault, F.: Contribution a l'étude de la fréquence de la tuberculose chez les alcooliques. Thèse de Paris, 1901. Imbault found that tuberculosis was about as common among the children of alcoholic parentage as among those of tuberculous parents.

Hodge, in 1897, obtained similar results. From one pair of alcoholic dogs he obtained twenty-three pups, eight were deformed and nine were born dead, while only four lived. In a control set forty-one individuals lived, four were deformed and there were no still-births.

Laitinen treated rabbits and guinea-pigs with various doses of alcohol and studied chiefly the changes in body conditions as to resistance against disease toxins, etc. He has also recorded observations on the offspring produced by these animals during the experiment. He is apparently more interested in the problem of the misuse of alcohol than in the scientific study of the influence of injurious substances on the offspring and in his enthusiasm to prove the point with extremely small doses of alcohol he fails to fully consider both sides of his own tables.

He used daily doses of alcohol as small as 0.1 c.c. per kilo of animal weight. This would amount to a small glass (200 c.c.) of beer per day for an adult man. His tables on careful study fail to show that so little alcohol actually does injure the offspring of the treated animals.

With alcoholized rabbits Laitinen finds that only 38.71 per cent. of the young live, while 61.29 per cent. are still-born or die shortly after birth. In the control, however, only 45.83 per cent. lived, while 54.17 per cent., more than half, were still-born or died shortly after birth. The animals were kept all together in a general cage and the pregnant females were only separated shortly before the young reached term. This is scarcely an approved method in breeding experiments, and the fact that young rabbits are so delicate and are born in a rather poorly developed state makes their careful handling necessary. The fact that more than half of the control young die, 54.17 per cent., would indicate the danger of drawing conclusions from a death-rate only 7 per cent. higher among the offspring of the treated animals.

The case of the guinea-pigs is also indifferent, 78.26 per cent. of the control young lived, while 21.75 per cent., or a little more than one-fifth, of them died. The large majority of the young of treated parents also lived, 63.24 per cent., while 37.76 per cent. died. In both sets more of the young lived than died. Guinea-pigs are easily reared and are born in a well-developed condition. On the other hand, in both of the rabbit sets more of the young died than lived.

Results which I shall record below show that larger doses of alcohol do produce definite effects on the offspring. My experiments have been performed in a different manner and from another point of view. The primary object has been to regulate or control the type of development in mammals in a definite fashion as I had succeeded in doing with lower vertebrates. In these experiments it will be demonstrated that an alcoholized male guinea-pig almost invariably begets a defective offspring even when bred to a vigorous normal female.

Rösch was the first to study the reproductive glands of alcoholics, in 1837, and found degeneration of the testicles. Lancereaux described a parenchymatous degeneration of the seminal canals. Simmonds (1898) found azoospermia in 60 per cent. of cases of chronic alcoholism; 5 per cent. of these men were sterile. Kyrle reported three cases of total atrophy of the testicular parenchyma in which death had resulted from cirrhosis of the liver due to alcohol. Kyrle attributed the atrophy of the testicle to the cirrhosis of the liver and not to chronic alcoholism.

Bertholet (1909) made an extensive examination of the influence of alcohol on the histological structure of the germ glands, more particularly on the testicles of chronic alcoholics. He found testicular atrophy in alcoholics with no cirrhosis of the liver. Bertholet observed partial atrophy of the testicles in the majority of seventy-five chronic alcoholics. These men died between the ages of 24 and 57 years, the greatest mortality being between 30 and 50 years. In thirty-seven cases, excluding syphilitics, a microscopical examination showed a more or less diffuse atrophy of the testicular parenchyma and a sclerosis of the interstitial connective tissue. The testicles were small and hard. The canals were greatly reduced in size and their lumina obliterated. Spermatogonia were atrophic. It was generally impossible to differentiate spermatocytes or spermatids. There were no dividing cells and no spermatozoa. The thick basal membrane of the canals was formed of connective tissue lamellæ with concentrated spindle cells. These conditions with slight variations were found in twenty-four cases. Such atrophic structures were already present in a drinker only 29 years old. In four cases of cirrhosis of the liver the testicular atrophy had not progressed very far and spermatozoa were still present. In five cases the microscopical conditions were less marked.

While these appearances of the basal membrane may also be observed in non-alcoholics, the extreme conditions of atrophy of the testicles were only found in alcoholics. Observing the testicles of non-alcoholics that had died of various chronic illnesses such as tuberculosis, no atrophy of the testicles or thickening of the membrana propria was found. Two such old men of 70 and 91 years still possessed spermatozoa in the canals. Bertholet concludes that the atrophy he has observed cannot be due to old age, but is due to the hurtful effects of chronic alcoholism on the reproductive glands.

Bertholet has also reported an atrophy of the ovary and ova in female alcoholics. Weichselbaum has confirmed the observations of Bertholet at his institute in Vienna.

Bertholet's observations are most important and his drawings bear out his statements. On the other hand, it is certain that the chronic alcoholic is not so often rendered sterile as his study might lead one to

believe. Judging from the statistics it is not rare to find alcoholics with large families. My experiments on animals may not be of sufficient duration at the present time, yet I have male guinea-pigs that have been almost intoxicated on alcohol once per day for six days a week extending over a period of nineteen months. These animals are still splendid breeders. Nineteen months of a guinea-pig's existence is proportionally equal to a good fraction of a human life. Many of these animals have been killed and their testicles examined microscopically and found to be normal. In some cases where a male had failed to succeed in impregnating the female for several times, he was partially castrated, one testicle being taken out. In this case the testicle was found to be normal and the same male has since given offspring by other females. Ovaries have been examined in a similar way, and in no individual has the alcohol treatment caused a visible structural change in the reproductive glands. The actual physiological proof of the efficiency of the organs is shown by the ability of all animals to reproduce. The important point which I shall show in the following pages is that although there is no visible structural change in the germ-cells, nevertheless, they have been modified chemically to an extent sufficient to cause them to give rise to defective embryos or weakened individuals which die shortly after birth.

Schweighofer has recorded an interesting individual case. A normal woman married a normal man and had three sound children. The husband died and she married a drunkard and gave birth to three other children; one of these became a drunkard, one had infantilism, while the third was a social degenerate and drunkard. The first two of these children contracted tuberculosis, which had never before been in the family. The woman married a third time and by this sober husband she again produced sound children. This is an important human experiment. The female was first tested with a normal male and gave normal offspring; when mated with an alcoholic male the progeny were defective as a result of his poisoned condition. She was again tested with a normal male and found to be still capable of giving sound offspring. A number of such cases are on record.

Schweighofer states from a mass of observations that the offspring of drunkards, themselves of good sound families, show much degeneracy and defective conditions.

Other substances than alcohol seem to act directly on the germ-cells of mammals. Constantine Paul long ago pointed out that the children of people working in lead were often defective. He made the interesting observation that when the father alone was employed in such work his children were affected by it.

All of the above experiments and observations refer more particularly to the action of injurious substances on the germ-cells of the male parent.

This is the crucial proof of an effect on the germ cells. The case of the female is complex, since the substance may produce a germinal defect by acting on the egg, or it may also directly affect the developing embryo and thus act as an environmental influence on development.

THE FEMALE GERM-CELLS AND THE DEVELOPING EMBRYO

Herbst's classical lithium experiments show the influence of salt solutions on developing eggs. The experiments of J. Loeb on fish embryos, those of Morgan on the frog and my experiments on fish all show the marked influence of inorganic salts and organic compounds on the development of the embryo. I showed that alcohol caused all known

TABLE 1.—EFFECTS OF WORKING IN LEAD

	No. of Cases	No. of Pregnancies	Abortions, Pre-mature Labor, Still-Births	Living Births	Remarks
Females showing lead poisoning symptoms..	4	15	13	2	One of the living children died in 24 hours
Females working in type foundry; previously had normal pregnancies	5	36	29	7	Four died in first year
Female in type foundry; five pregnancies	1	5	5	0
Females working intermittently; while there	3	3	3	0	After being away for some time had healthy children
Females with blue line on gums, only sign of poisoning	6	29	21	8
Male alone exposed.....	?	32	12	20	8 died first year, 4 second year, 5 third year
Total.....	..	120	83	37	22 died under three years

gross abnormalities of the brain in fish embryos and also gave all possible abnormal conditions of the eyes. Other substances such as ether, chloroform, chlorbutanol (chloretone), etc., also had a peculiar affinity for the developing central nervous system. These substances also act physiologically on the central nervous system of the adult.

Constantine Paul not only showed the injurious effects of lead on the paternal germ-cells, but also recorded instructive data regarding the offspring of women working in lead. More recent observers have pointed out the frequency of idiocy and other defects among the children of lead workers. Adami has tabulated the findings of Constantine Paul as shown in Table 1.

Forel states that acute alcoholic intoxication affects not only the brain, but, as Nicloux has shown, the alcohol passes quickly to the cells of the testicle or ovary and Bertholet's observations confirm this. A conception which takes place while the cells are in this poisoned state often results in a feeble-minded or degenerate child. The facts furnished by experiments on the eggs and spermatozoa of lower animals lend the strongest support to this idea and there is no experimental evidence that can be interpreted as opposed to Forel's statement.

Chronic alcoholics who consume daily certain amounts of alcohol slowly injure their germ cells. By intensive use of alcohol these cells may actually be killed or caused to atrophy. This, however, is the extreme case and before reaching a state of atrophy the cells pass through various grades of defectiveness. The stages may show no anatomic changes, but their physiologic state is indicated by the defective individuals to which they give rise in development.

Bezzola found that in Switzerland, in the years 1880 to 1890, there were 8,190 idiots. Most of the idiots were born in wine districts, and the season for the maximum birth of such children was nine months after the great national feasts, indicating, possibly, that idiots were conceived during the period of heaviest drinking. Schweighofer found the same relationship between the season for the greatest number of still-births and the feast seasons in Austria.

Martin studied the family histories of eighty-three epileptic girls in the Salpêtrière (Paris). Sixty had alcoholic parents, while of the other twenty-three alcoholism was doubtful or absent in their parents. The sixty girls from alcoholic parentage had 244 sisters, of them 132, or 54.1 per cent., were dead; forty-eight, or 19.7 per cent., had had spasms during childhood.

Studying the direct ancestry of 370 insane people, Jenny Koller (in 1895) found that there were twice as many drinkers as were found in the direct ancestry of 370 sound people selected at random. Others have recorded similar observations.

Karl Pearson and Miss Elderson studied statistically 3,000 school children in England. They concluded that the children of alcoholics were often heavier than those of sober parents, they were also less diseased, had little epilepsy and tuberculosis and are actually cleverer in school. They found, however, a greater mortality among the children of alcoholics, especially of female drinkers, and concluded that only the stronger children lived, and therefore, their quality was good.

These studies have been widely criticised, and are probably not based on very thorough biological observations. They consider, in the first place, only school children. It is not known whether the parents were drunkards at the time of, or previous to the conception. The degenerate

offspring of alcoholics could not enter school. The results would doubtless have been quite different if the inmates of an institution for defective children had been studied. The great body of evidence from anatomic studies of the reproductive glands of alcoholics, the animal experiments and disease records are all opposed to Pearson's conclusions.

The most valuable study that I have been able to find on the influence of alcohol on the human offspring is that of Sullivan in 1899.

Sullivan emphasizes the point that while much effort has been made to record alcoholism in the ancestry of degenerates, the important study must be made on degeneracy in the descendants of well-observed alcoholics. He studied the alcoholics among the female population of the Liverpool prison and as far as possible chose cases of alcoholism that were unaccompanied by disease or other degenerate factors.

Localization of alcoholic lesions in the body are not well worked out, yet it is unquestionable that in the criminal, as in insane alcoholics, the nervous manifestations of the intoxication occur with notable frequency, while non-nervous disorders are rare or secondary. Of these alcoholic females, thirty-one had had one or more attacks of alcoholic delirium, twenty-four had occasional hallucinations, suicidal impulses; disorders of cutaneous sensibility, and cramp in the extremities was noted in a considerable number of cases. In these patients tissues other than the nervous, so far as examination of the patients themselves could show, were comparatively immune to the poison of alcohol, and this was also true of their alcoholic relatives.

There were 100 women in the series Sullivan observed, and twenty of these gave details of female relatives of drunken habits who had children. To these 120 females were born 600 children, of whom 265, or 44.2 per cent., lived over two years; 335, or 55.8 per cent., died under 2 years or were still-born. Twenty-one of the women observed gave records of sober relatives, sisters or daughters married to sober men. The twenty-one drunken females had 125 children, sixty-nine, or 55.2 per cent., died under 2 years; the twenty-eight sober females had 138 children, and thirty-three, or 23.9 per cent., of them died under 2 years. The death-rate of children from the drunken mothers was nearly two and one-half times greater than that of the children of their near-blood relatives who were non-alcoholic. The alcoholics, however, are poor mothers and take little care of their children; this fact might possibly account for the entire difference, though such a deduction is extremely improbable.

The progressive births in the alcoholic family show interesting records. In eighty cases the number of children reached or exceeded three.

The tabulation shows an increasingly poor condition. The records of two individual cases may be mentioned by way of illustration:

Case 5: Three first children healthy, fourth of weak intelligence, fifth epileptic idiot, sixth still-born, and finally an abortion.

Case 10: First child survived to adult life, second died of infection as child, two infants then died in convulsions in first few months, then a still-birth.

These records stand in interesting contrast with those known for syphilitic mothers in which each conception seems to be more and more nearly successful until a weak offspring is born, and finally such a mother may give birth to an apparently normal child. The syphilitic is gradually becoming less diseased and is overcoming the toxic condition as time goes on, while these alcoholic women are on the contrary becoming more and more saturated with the poison, and for this reason each succeeding birth is more decidedly defective.

TABLE 2.—SHOWING PERCENTAGE OF STILL-BORN AND CHILDREN WHO DIED IN AN ALCOHOLIC FAMILY

	Cases	Died or Still-Born, Per cent.	Still-Born, - Per cent.
First born	80	33.7	6.2
Second born	80	50.0	11.2
Third born	80	52.6	7.6
Fourth and fifth born	111	65.7	10.8
Sixth to tenth born.....	93	72.0	17.2

The records were worse for women who had begun drinking some time previous to the first conception. In thirty-one cases they had been drinking for at least two years before the first pregnancy. Of 118 children born to these, seventy-four were still-born or died in infancy, giving 62.7 per cent. as compared with a death-rate of 54.1 per cent. for the others of the series.

In only thirty-nine of the cases were the women's parents sober people, yet the records of the offspring from these women were equally as bad as those from the sixty-one mothers who had alcoholic parents. This is a significant fact, since it indicates most strongly that the defective children are due to the direct effect of alcoholism and not to other degenerate conditions. Sullivan recorded seven known cases of conception during a state of drunkenness; six of the children died in convulsions in a few months, while the seventh was still-born.

Another observation by Sullivan which indicates that the alcohol as such is the cause of defectiveness was the fact that mothers imprisoned during pregnancy gave birth to a better child since the drinking was stopped.

Sixty per cent. of the children of all these mothers died in convulsions. This is a common manner of death for the offspring from the alcoholic mammals I have studied.

Kende found that of twenty-one families in which the father and mother both drank, ten were childless, while of the twenty-four children in the other eleven families, sixteen died early and only three were entirely normal. In eighteen families in which only the father drank, but three children in twenty-one were entirely sound, while there were many abortions and several cases of sterility.

There are numerous statistical facts showing a large percentage of alcoholics in the ancestry of prostitutes, degenerates and other inferior classes. All of the studies seem to show that alcoholism and the degenerate condition tend to occur in the same family, and Sullivan seems to control the case by showing that in some instances, at least, alcohol is the cause of degeneracy.

The real, crucial proof of the direct action of alcohol must come, however, from experiments on lower animals, where the sources of error may be entirely controlled.

Adami states: "The general belief (and we regard it as well founded) is that the children of the sot are as a body of lowered intelligence and vitality with unstable self-control." He recognizes the great difficulty of statistically proving this in man, since alcoholism is so often the accompaniment of weakness and hereditary taint, and may not be the primary cause of the condition in many families. With animals, however, the experimenter is enabled to prove that alcohol does induce a primarily degenerate condition.

One could continue to enumerate records showing the effect of alcoholism on the human offspring, yet a sufficient number of studies have been considered to show how strongly indicative the evidence is that alcohol is really the direct cause of defects in many cases. There is also little doubt that alcoholism is sometimes acquired by perfectly normal human beings, and when the tissues of such people become affected by alcohol they no doubt give rise to defective and abnormal offspring.

It is, however, an undeniable fact that alcoholism in man is very frequently an accompaniment of various degenerate conditions, and these conditions are oftentimes within themselves sufficient to account for further degeneration in the offspring. We shall, therefore, consider more fully at this point the evidence furnished by animal experimentation.

ANIMAL EXPERIMENTS

As stated above, the problem is broader than the subject of alcoholism. If it is shown that any toxic substance can act on the germ cells or developing embryo in such a manner as to change or modify its

development, it necessarily follows that alcohol may induce a more or less equivalent condition, since it is definitely known to act on all animal tissues. I shall, therefore, mention the experiments with alcohol in particular, and at the same time consider other of the striking examples of environmental effects on the developing eggs of lower animals.

H. E. Ziegler treated sea-urchin's eggs with ethyl-alcohol. A 1 per cent. solution in sea-water delayed development, a 2 per cent. solution also delayed development and caused abnormal embryos, while a 4 per cent. solution prevented all development. The peculiarly typical larvæ of the sea-urchin which Herbst induced by the addition of lithium salts to sea-water have been mentioned above. Herbst's experiments furnish a striking example of a characteristic response on the part of the developing organism to a definite chemical treatment. Morgan obtained similarly definite results by treating frog's eggs with lithium, and I have shown a somewhat comparable response for the fish's egg. Other salts may give the same types of larvæ, as occurred in these cases, as McClendon has shown for the fish, and as I previously pointed out in several of my studies on the cyclopean defect. Yet with certain doses of given substances one gets greater numbers of the same defect than with any other treatment. It is not surprising that a few individuals of any one deformed type may occur in a number of different solutions. The important fact is, that with a particular treatment one is able to obtain on all occasions a large number of embryos exhibiting a perfectly clear-cut, definite defect.

Ridge got decided results by treating the eggs of the blue bottle-fly and frogs with alcohol. In solutions of 1/100 per cent. alcohol in water the development was slow. In 1/20 per cent. solutions development proceeded for only a short time and the eggs died. In one per cent. alcohol only one or two eggs started.

Ovize made an interesting observation on the influence of alcoholic fumes on developing hen's eggs. An incubator containing 160 eggs was in a cellar in which wine and brandy were being distilled. Seventy-eight chickens hatched; of these twenty-five were deformed and forty died during the first three or four days. Of the number unhatched, one-third were deformed, and 3 to 4 per cent. had only developed a short way.³

Féré has experimented extensively with the influence of alcohol on the developing hen's egg. Alcohol was injected into the albumen in some experiments, while in others the eggs were placed under bell jars and exposed to the fumes of evaporating alcohol. Enough of the fumes penetrated the shell and entered the egg to affect the subsequent development of the embryos. When eggs were placed in the incubator after such

3. These results by Ovize were taken from Forel's review.

treatment they developed more slowly than the control and a large number of malformed embryos resulted. The abnormalities were variable, yet many had defective nervous systems and a number of the embryos exhibited eye defects. Féré made no attempt to analyze the cause of the different types of deformities, and in fact he paid little attention to the structure of the defects. Yet he showed most decidedly that alcohol fumes do affect the developing embryo, as one might have inferred from the preceding observations made by Ovize.

I have repeated Féré's experiments at some length during the past two years and can confirm his results. My object has been to regulate the treatment in such a manner as to get definite types of defects with certain intensities of treatment. Up to the present time I have only partially succeeded in doing this, though in several experiments the delay in development and the general type of the defects has been rather constant. This treatment of hen's eggs with alcoholic fumes is one of the most convincing and easily performed demonstrations of the influence of alcohol on development.

Féré also experimented with hen's eggs to show the influence of differences in temperature during incubation and many other physical and chemical factors. All unusual conditions affected the development of the embryo. Féré also developed hen's eggs in glass dishes after removing them from the shell. Preyer and Loisel had previously done similar experiments, but they carried the embryo for only a day or so, while Féré succeeded in keeping the egg developing for six days. Some of these embryos develop abnormally.

I have recorded a number of experiments on fishes' eggs which show the decided effects of alcohol and a large series of other substances on embryonic development. Alcohol and various anesthetics showed a peculiar affinity for the developing nervous system and organs of special sense. In many cases other organs and parts of the embryos were apparently normal. Many of the deformed individuals hatched and lived for some time, swimming about and feeding in a typical fashion.

With alcohol solutions of given strength definite defects were induced. In some experiments dozens of embryos with typical brain and eye defects occurred, while few or no other types of deformities existed. *The experimenter has the power in these cases to predict with at least a limited degree of certainty the type of deformity which will result from a definite intensity of a particular treatment.* Embryonic development in such cases may really be regulated or controlled.

We have already considered a number of experiments on mammals' which show that alcohol and other injurious substances affect the quality of the offspring. In treating mammals the case is not so simple as in treating the eggs of lower vertebrates which develop outside the

parent's body. The effects in mammals may not be due directly to the substance used, but rather indirectly to the changed conditions the substances have induced in the body of the parent. It is important for this reason to know whether certain substances come in direct contact with the germ cells of the individual. As before mentioned, Nicloux and Renault have shown that alcohol may be readily found in the seminal fluid of a man shortly after drinking it. Thus the spermatozoa may come to float or swim in a weak solution of alcohol.

In the case of female mammals, Nicloux has carefully demonstrated the passage of alcohol from the blood of the mother into the tissues of the embryo. The following tabulation readily shows the results of his experiments on dogs and guinea-pigs:

TABLE 3.—PASSAGE OF ALCOHOL FROM THE MOTHER TO THE FETUS

		Amt. of Abs. Alc. Inject. per Kilo of Animal Weight, c.c.	Time of Absorption; Animal Killed, Hours	Amt. Alc. per 100 c.c. Maternal Blood, c.c.	Amt. Alc. per 100 c.c. Fetal Blood, c.c.	Amt. Alc. per 100 gm. Mother's Liver, gm.	Amt. Alc. per 100 gm. Fetal Tissue, c.c.
1.	Guinea-pig	5	5/6	0.36	0.31
2.	Guinea-pig	5	1	0.47	0.35
3.	Guinea-pig	2	1	0.20	0.10	0.12
4.	Guinea-pig	1	1	0.13	0.081	0.086
5.	Guinea-pig	0.5	1¼	0.045	0.015	0.02
6.	Dog	3	1½	0.37	0.37	0.26	0.26

After a short period of time the amount of alcohol in the blood of the fetus is about equal to that in the blood of the mother, while there is really more alcohol in a given weight of the tissues of the fetus than is to be found in an equal weight of liver tissues from the mother.

The reality of the passage of alcohol from the mother to the fetus demonstrates the possibility of the intoxication of the fetus. Therefore, nervous disorders, anesthesia, etc., of the late fetus may result as a consequence of alcohol in the blood, while the developing embryo or early fetus will show the effects by an abnormal formation of the nervous system.

Thus the results of the experiments of Mairer, Combemale and Hodge on dogs are readily explained as the direct influence of alcohol on the paternal germ cells in the case of the treated male, or on the developing fetus within the body of the alcoholic mother. The great number of human records briefly referred to above are also readily interpreted as the result of direct alcoholic action on the germ cells and the developing embryo.

The experiments on mammals do not then really differ greatly from those on the lower vertebrates where the externally developing eggs are placed directly in various unusual solutions, since the egg or embryo although within the mother's body is readily bathed or impregnated by the alcohol contained within the mother's blood.

The only experiments with alcohol on lower mammals which do not fall completely in line with the above records are those recently recorded by Nice. He has fed mice on alcohol. Each day 2 c.c. of 35 per cent. alcohol was added to crackers and milk and placed as food for each mouse. Instead of drinking water the mice could drink 35 per cent. alcohol from a syphon which prevented evaporation. Animals treated in this way gained in weight over the control. The offspring from these alcoholic mice excelled all the other mice in growth, even when they themselves were fed alcohol. The young grew faster, however, when not given alcohol. Nice treated other mice with tobacco fumes, nicotin and caffenin. The fecundity of the alcohol, nicotin and caffenin mice was greater than the control while those treated with tobacco fumes had almost twice as many young as the control. The mortality of the offspring from the treated mice was, however, greater than from the control. None of the control young died, while 17.3 per cent. of the nicotin young and 11.1 per cent. of the alcoholic young died soon after birth. There was only one abortion, no still-births and none of the young were deformed.

Mice may possibly be peculiarly resistant to these drugs, though I should rather think that in the case of alcohol, at least, the animals received too little to give a pronounced effect, though it was sufficient to cause a certain fatality among the young. Weak alcohol mixed with crackers and milk no doubt rapidly evaporates. The animals possibly waited until a certain amount of the alcohol had disappeared before they ate their food, and, of course, the amount of alcohol they took instead of drinking water was very small. Mice may easily be kept on a cracker and milk diet without ever receiving water. One cannot deny, however, that the mice did receive enough alcohol to cause them to fatten more rapidly than the control, and probably to cause the death of some of their offspring.

Carrière has shown that when guinea-pigs are inoculated with various soluble products of the tubercle bacillus for several months that the number of offspring is diminished. He sometimes observed the death of the fetus or premature death of the young, while many of the living young had feeble constitutions. The action was produced when either parent was impregnated with the poison.

Mating together two inoculated animals gave 52 per cent still-born young; 28 per cent. of the living young died under sixteen days and

only 20 per cent. of the young survived. When the female alone was inoculated 26.9 per cent. of the offspring were still-born, 34.6 per cent. died under sixteen days and 38.4 per cent. of the young survived. The matings with the male alone inoculated gave 16.6 per cent. still-born, 10 per cent. dying under sixteen days and 73 per cent. of the offspring survived. Thus the effect of the toxin is shown on the germ cells of both sexes.

Lustig's experiments of inoculating fowls with abrin gave results parallel to those recorded by Carrière. The offspring were less resistant to inoculations of abrin, just as the guinea-pigs were to the tuberculosis extracts when compared with control animals of the same age.

Mall has clearly shown in his monograph on the causes of human monstrosities that poor nutrition and abnormal environment are most potent factors. Only 7 per cent. of the uterine pregnancies examined gave monsters, while 96 per cent. of the tubal pregnancies produced abnormal embryos.

Ballantyne has presented in his "Antenatal Pathology" a most comprehensive consideration of the part played by abnormal environment and disease in the causation of monstrosities and developmental defects in general.

The effects of malnutrition or poor environment on the developing embryo is splendidly illustrated by the case of monochorial twins when one becomes more vigorous and pumps blood from the other through the anastomoses between their placental or umbilical vessels. In such cases one of the twins may fail to develop certain parts and may actually lack a heart, the heart of the superior embryo pumping blood through both the bodies. The various degrees of the degenerate or parasitic twin is thus produced. One individual falls behind in development and may finally actually be included within the body of the more vigorous twin. Double monsters may occur in which one individual is almost perfect, while the smaller monster is attached to some part of its body.

I have given this somewhat extensive survey of the literature in order to show that an abundance of evidence exists at the present time to indicate that the course of embryonic development may be readily modified. It is also clearly shown that the germ cells of various animals may be directly affected by different chemical treatments to such a degree that they give rise to defective individuals. The experiments of O. Hertwig and Morgan on the chemical production of spina bifida in large numbers of tadpoles and my experiments on the constant production of typical cyclopic monsters by subjecting developing fish eggs to definite chemical treatments strongly indicate that the manner of embryonic development may be definitely regulated. This exact regulation or control of development is the important goal of experimental teratology.

The problem is now in its beginning, since the actual influence of various treatments is known to be expressed in the resulting type of embryonic development.

The studies on alcoholism in mammals have failed to produce any convincing evidence of the specific actions of this poison. Yet the statistical studies on defective human beings would indicate that alcohol had a special affinity for the developing nervous system. My experiments on the influence of alcohol on the developing fish embryo demonstrated that alcohol did have a specific affinity for the central nervous system, and caused the brains of these embryos to exhibit numerous deformities, while the organs of special sense were also affected.

METHOD AND RESULT

The experiments here recorded have been undertaken in order to ascertain whether alcohol did exert a marked influence on the germ cells and developing embryos of mammals, and, if possible to demonstrate the nature and mode of action of this influence. I have used alcohol as an agent, since it may be given to guinea-pigs without greatly disturbing their normal physiological processes, and so does not produce marked conditions which might secondarily affect the results. Alcohol may remain as such in the blood and tissues of a mammal, and so may act directly just as it would when added to the sea-water in which fishes' eggs were developing. I have studied its effects experimentally on the eggs of lower vertebrates and am familiar with the defects it produces in these animals. It is an active substance and, therefore, for these many reasons lends itself admirably to experimental use.

The experiments have been conducted on guinea-pigs, since they breed fairly rapidly and rear their young without much difficulty in the laboratory. Strong healthy stock has been chosen and the animals have been carefully handled. All have remained in vigorous health and most of them have increased in size and fattened during the progress of the experiment. The males and females have been kept carefully separated and individual pairs mated from time to time.

The animals are first tested by normal matings and found to produce normal offspring. The alcoholic treatment is then begun on a given number of individuals and males and females mated in different combinations according to whether they are alcoholics or normal. An alcoholic male is mated with a normal female, the paternal test. This is the crucial test for influence on the germ cells, as here the defective offspring must be due to the chemically modified spermatozoon from which it arose, since the egg, and the mother in which the embryo developed, were both normal.

Normal untreated males are paired with alcoholic females, the maternal test. Here the defective offspring may be due either to a modified ovum or to the fact that it developed in a mother with alcoholic blood, therefore supplying an unfavorable developmental environment. Lastly, its condition may be due to both of these causes. The mammalian mother has two chances to injure an offspring, either by producing a defective egg, or secondly by supplying an unfavorable or diseased environment in which the embryo must develop.

The final combination is the mating of alcoholic individuals. This, of course, offers the greatest chance for defective offspring.

Alcohol is administered to the guinea-pigs by inhalation. At first it was given with the food, but the animals did not relish it, and therefore took less food. It was then given by stomach tube, but this method

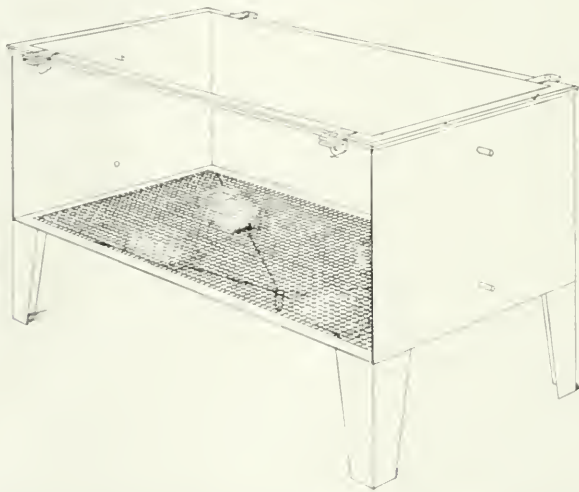


Fig. 1.—Tank for alcohol treatment. Animals are placed on the wire screen in the closed tank and inhale the fumes of alcohol evaporating from the cotton below the screen.

so upset the animals that the results might have been modified by their poor bodily condition and the bad state of their stomachs. The inhalation method is entirely satisfactory, the guinea-pigs thrive and usually gain in weight during the experiment, they have good appetites and are in all respects apparently normal. The only indication of the effects of the treatment is shown by the quality of offspring they produce.

The apparatus used for giving the alcohol consists of an air-tight copper tank 36 inches long by 18 inches wide and 12 inches deep, with a sloping bottom draining to the center. Over this bottom is placed a wire screen and below the screen cotton soaked with 95 per cent. alcohol is spread (Fig. 1). The tank is closed and allowed to stand until the

atmosphere within is saturated with alcoholic fumes. A ventilation system is so arranged that a given quantity of alcohol fumes may be driven through the tank in a given time, but it has not seemed advisable to use this device, as the degree of intoxication is a better index to the physiological response of the animals, since their resistance to a given amount of the fumes is changeable. The guinea-pigs, three or four at a time, are placed on the wire screen above the evaporating alcohol, the tank is again closed and the animals are allowed to remain until they begin to show signs of intoxication, though they are never completely intoxicated. They usually inhale the fumes for about an hour. The animals are treated in this way for six days per week and some have now been treated over a period of about nineteen months. None of the effects

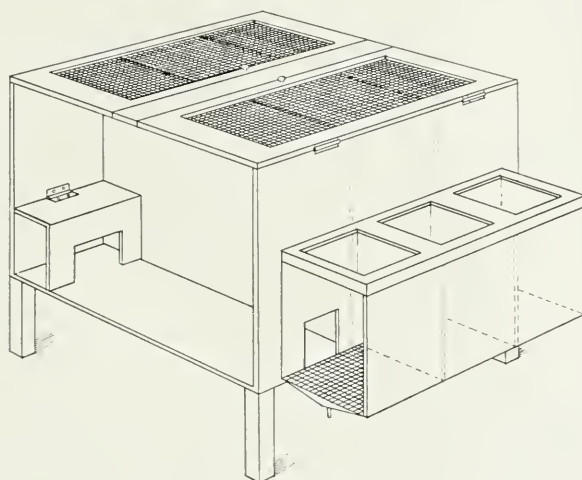


Fig. 2.—Breeding cage with fume tank attachment. Pregnant females are kept in this cage and may be driven through the drop door into the fume tank. Handling pregnant animals during the treatment is thus avoided.

are due to want of air, since the same number of guinea-pigs may remain for hours in this closed tank without showing any signs of discomfort when there are no fumes present.

In order to avoid handling the females during late pregnancy, a special treating cage is devised for them. An ordinary box run with a covered nest in which the animal lives is connected by a drop door with a metal-lined tank having a similar screen arrangement to that described for the general treatment tank (Fig. 2). The pregnant animal may be driven daily into the tank and thus treated with alcohol fumes throughout her pregnancy without having to be handled or moved about in any way that would tend to disturb the developing fetus.

During the vapor treatment the animals usually react in a manner quite similar to their behavior in weak fumes of ether or chloroform.

The majority of them sit quite motionless and sniff their noses for a time and then become somewhat drowsy. A few individuals, however, are excited by the treatment and run about the tank, becoming sexually excited, and many often fight other animals savagely. One of the males fights and bites so vigorously while taking the fumes that he has to be treated separately from all others. The fumes then have a different influence on the behavior of different individuals in much the same way that alcoholic intoxication expresses itself differently on different human beings.

During the first few weeks of the treatment the fumes cause the eyes to water so that tears run over the face. The nose and mouth also become moist and the animals sniff almost constantly. The fumes are very irritating to the mucous membranes at first. The cornea becomes irritated and finally opaque in some instances, so that the eye takes on a white appearance. The tissues seem, however, to develop a resistance to the fumes. The eyes become clear after a few months and never again become opaque. The nasal mucosa also ceases to secrete excessively unless the animal is left in for an unusually long time.

Many of the guinea-pigs have been killed after treatments of different duration up to fifteen months, and all of their viscera carefully examined. In no case have I found any changed structures due to the alcoholic treatment. The lungs, liver, stomach, intestines, kidneys, reproductive glands, brain and all other parts appear perfectly normal. The general health and behavior of the animals also indicate that they are in good condition. As before mentioned, several animals have been partially castrated during the experiment. One of the reproductive glands was removed and examined microscopically. In all cases the germ cells, ova or spermatozoa, as the case may be, were found to exhibit perfectly normal structure. One cannot claim, therefore, that this treatment is excessively severe or greater in proportional amount than the alcohol a human being often takes. The fact is that these animals have never been completely intoxicated, but receive only enough alcohol six times per week to affect their nervous states. They may be compared to a toper who drinks daily but never becomes really drunk.

While the bodies of these animals display no direct effects of the alcohol, the conditions of the offspring to which they give rise show most strikingly the effects of the alcoholic treatment. The results of mating the alcoholized guinea-pigs are summarized in Table 4.

Fifty-five matings of treated animals have been made. Forty-two of these have now reached full term and are recorded. Thirteen matings are not yet due. From the forty-two matings only seven young survived, and six of these are still living, five of which are runts, though their parents were unusually large, strong animals (Figs. 4 and 5).

The conditions of the animals in the mating pairs are shown in the first column of the table and the total results of the matings are indicated in the following columns. The first horizontal line gives the records when alcoholic males are paired with normal females. Twenty-four such matings were made. Fourteen of these gave negative results, or resulted in early abortions. Many embryos were aborted during very young stages, and some of these were deformed, though they were generally in such poor condition after being cast out into the cages that little could be learned from them. They were partially or completely eaten by the mother in most cases. The males were always kept for a number of days with the females during favorable periods, and conception should have occurred in all cases, as it did in the control matings.

TABLE 4.—EFFECTS OF ALCOHOL ON OFFSPRING OF GUINEA-PIGS

Condition of Animal	No. of Matings	No Result or Early Abortion	Still-Born Litters	No. Still-Born Young	Living Litters	Young Dying Soon After Birth	Surviving Young
Alcoholic male by normal female.....	24	14	5	8	5	7	5*
Normal male by alcoholic female.....	4	1	0	0	3	3 (a)	2‡
Alcoholic male by alcoholic female.....	14	10	3	6	1	1 (b)	0
Summary.....	42	25	8	14	9	11	7‡
Normal male by normal female—Control.....	9§	0	0	0	9	0	17

*Four survivors in one litter, and one was a member of a litter of three, the other two died immediately after birth. (a) Premature. (b) Sixth day.

‡One lived to become pregnant with two young *in utero*, one deformed, Fig. 3. Other survivor normal, the mother was not treated until after first two or three weeks of pregnancy.

§Of thirty-two young born only seven have survived.

§One other non-alcoholic mating was made from which two young resulted; they died after the second and fourth days, respectively, and the mother died two days later; her diseased condition no doubt affected the suckling young. They have for this reason not been included in the normal control.

Only ten of the twenty-four matings resulted in conceptions which ran the full term. Half of these, or five, were still-born litters. There were three still-born litters of two young each and two of one individual each. Most of these were slightly premature, their eyes being closed and the hair sparse on the bodies. (A normal guinea-pig at birth is well covered with a hairy coat, its eyes are open and it very quickly begins to run about actively.)

Five litters of living young were born. One litter consisted of only one young, a weak individual that grew very little and died after six weeks. Two litters contained two young each. The members of one of these litters died during the first and fourth weeks, having been weak and small since birth. Both of those in the other litter were in a similarly feeble condition and died before the first month. One litter contained three young; two of these died immediately after birth; the other one is still alive, though small for its age. The fifth litter contained four young, all of which are runts, though their parents were unusually large animals (Figs. 4 and 5). *Thus out of twenty-four full-term young, of which only twelve were born alive, but five individuals have survived, and these are unusually small and very shy and excitable animals.*

It is a point of some interest that all of the young animals that died showed various nervous disturbances, having epileptic-like seizures, and in every case died in a state of convulsion. This is commonly the fate of feeble and nervously defective children.

The important fact in the above case is that only the father was alcoholic, the mother being a normally vigorous animal. *This experiment clearly demonstrates that the paternal germ cells may be modified by chemical treatment to such a degree that the male will beget abnormal offspring even though he mate with a vigorous female.* A reconsideration of the figures in the first line of the table shows really how decidedly the injured spermatozoon expresses itself in the fate of the egg with which it combines.

The second line of the table shows the results of matings between alcoholized females and normal males. These matings might be expected to give more marked results than the previous ones, since in the treated females not only the germ cells may be affected, but the developing embryo itself may be injured by the presence of alcohol in the blood of the mother. Nicloux has shown that alcohol may pass directly from maternal blood into the embryonic tissues of a guinea-pig. The spermatozoon, however, is probably a more sensitive structure than the egg and is easily injured or killed by slightly abnormal conditions. It might possibly be that when such a specialized cell swam for even a short period of time in seminal fluid containing a trace of alcohol its chemical nature would be so decidedly disturbed as to render it incapable of inducing normal development after impregnating the egg. At any rate the few cases at present available seem to indicate that the effect on the offspring is equally as great when it is produced by an alcoholic father as by an alcoholic mother.

There are only four matings between alcoholized females and normal males. One of these gave a negative result or was possibly aborted very early. Three living litters were born. One of these consisted of three

premature young, which died shortly after birth. The remaining two litters each contained only one young, but these two animals survived. One of these guinea-pigs was born after the mother had been treated for three and one-half months. The offspring was weak and small for several months after birth, but finally recovered and developed into a normal animal. This guinea-pig was mated with an alcoholic male and became pregnant. Unfortunately, she was killed by accident, and on examination her uterus was found to contain two embryos, 33 and 32 mm. in length. One of these embryos was deformed and showed very decidedly

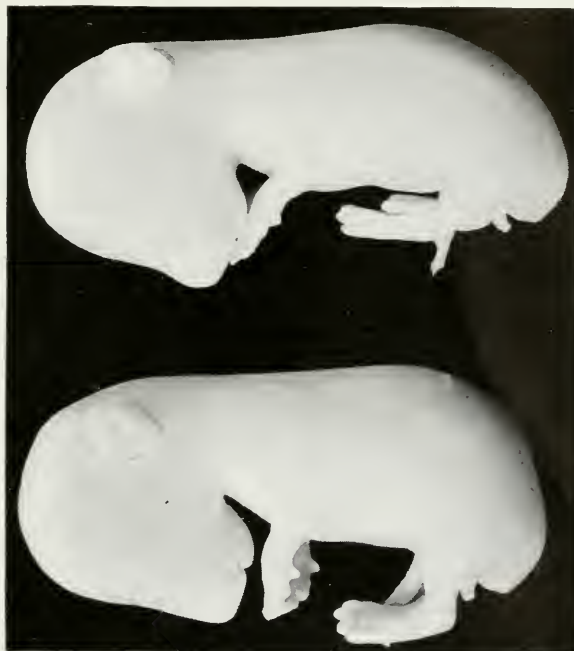


Fig. 3.—Two embryos 32 and 33 mm. in length, taken from a female that had an alcoholic mother and was mated with alcoholic male. The upper fetus has deformed hind legs and a poorly developed posterior part of the body; lower fetus is normal.

degenerate and feebly developed hind legs. The posterior end of its body was also poorly formed. This condition is readily seen in Figure 3, a photograph of the two embryos. The abnormal one has small hind legs, and one of them is badly folded under its body. This is of interest, since all of the affected offspring of alcoholic guinea-pigs are weak in their hind extremities and drag their legs. Yet none were so modified as to show a noticeable structural defect except this embryo, which had one alcoholic grandmother and an alcoholic father.

The only other survivor from an alcoholic mother is strong and full grown for its age. The mother had been treated for only two and one-half months when the offspring was born, so that she was normal during the first two or three weeks of pregnancy. No doubt the early stages of development are more easily modified to produce significant defects than are the later. This question is being more fully tested on guinea-pigs with experiments now in progress. I have shown, however, in

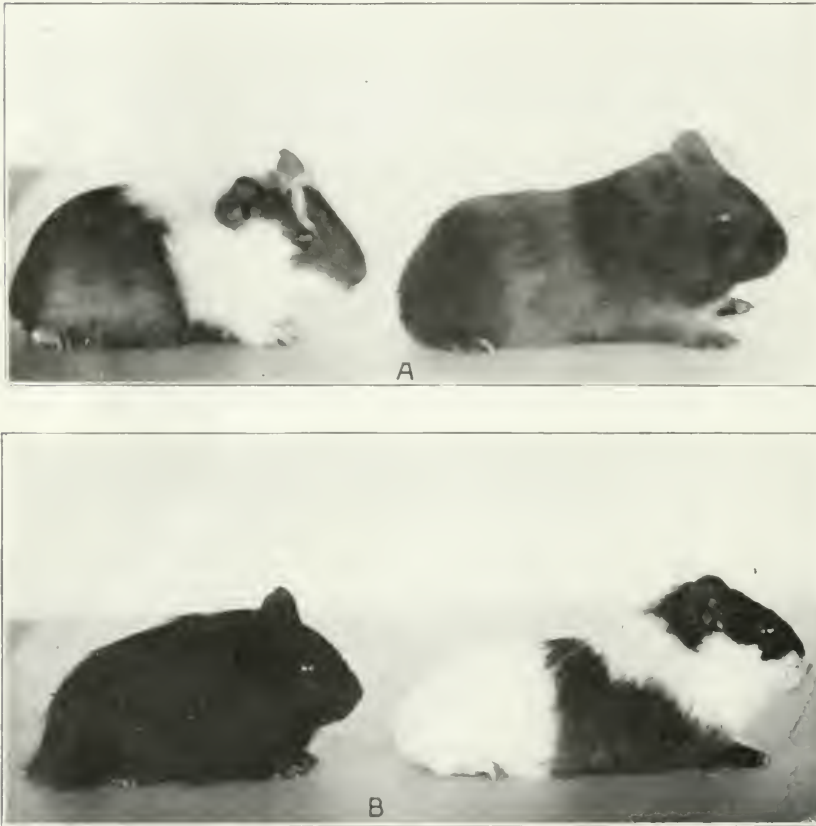


Fig. 1.—A. The animal on the left is a runt from a large alcoholic male and a large normal female; weighs 134 gm. The animal on the right, from normal parents, is larger although 1 month younger and weighs 147 gm.

B. The guinea pig on the left is a runt, weighing 132 gm. from an alcoholic father; on the right a normal guinea-pig twice as large though only 10 days older, weighs 221 gm.

treating fish eggs that the period at which the treatment is applied is a most important factor in determining the type of defect or modification which will result. Certain salts, different strengths of magnesium chlorid, for example, which give pronounced effects when added to the

sea-water containing eggs in early developmental stages, may really be ineffective after the eggs have developed beyond these stages. In the case under consideration the offspring might not have fared so well if the alcoholic treatment had been started on the mother a few weeks before conception, instead of three weeks after her pregnancy had begun. This with other points shall be more completely analyzed in future communications on these experiments.

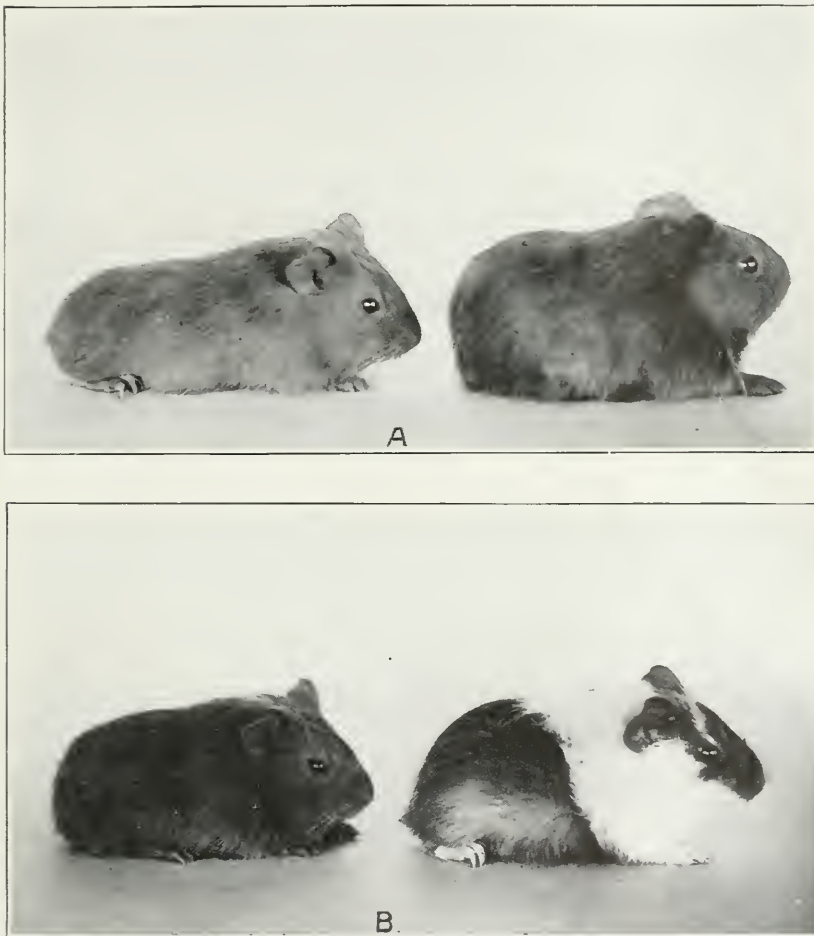


Fig. 5.—A. Two guinea-pigs from alcoholic fathers, the left one 1 month and 10 days younger than the runt on the right.

B. The left animal is the same as above, the right another of the same runt litter.

The four matings of alcoholic females and normal males resulted in three living litters in all of five individuals. Three of the young were premature and died shortly after birth, while two young survived.

Finally, we may consider the results of pairing two alcoholized individuals. The third line of the table summarizes these results. As might have been anticipated, this type of mating has given the highest fatality of all.

Ten out of a total of fourteen matings have given no offspring or early abortions, which were in many cases eaten by the mother. Three still-born litters have been produced, each consisting of two young. *Only one living litter was born from the fourteen matings in which both parents were alcoholic, and this litter consisted of but one weak individual which died in convulsions on the sixth day after birth.* This is indeed a decided effect of alcohol on the offspring when one compares it with nine control matings, all of which gave living litters containing a total of seventeen individuals, all surviving.

Two other young were produced by non-alcoholic parents and died on the second and fourth days after birth. They have not been included in the control since the mother died two days later in a diseased condition. No doubt the poor state of the mother had much to do with the fate of the suckling young. She was an animal that had only been in the experiment for a short time, and is one of the very few that have contracted disease or died during the nineteen months of the work. This might possibly go to show the influence of a diseased mother on the offspring.

The fourth line of Table 1 gives a summary of the experiments. There have been forty-two full-term matings, twenty-five of which gave no results or early abortions; eight still-born litters have occurred, consisting of fourteen individuals; only nine living litters have been born, 21 per cent. of the matings. These contained eighteen young, and but seven of this number have survived and five of these survivors are unusually small (Figs. 4, 5).

The bottom line of the table shows nine control matings. All have given living litters containing a total of seventeen young, all of them surviving. The two young that died, as stated above, were from a dying mother and not included in the control.

Records of the successive matings of ten of the female guinea-pigs are shown in Table 5. The varying ways in which the same individual has responded in different matings is noticeable. Number 10, an alcoholic female, first mated with an alcoholic male, gave one young which died on the sixth day after birth. On being remated with the same male, No. 10, gave no result. When mated with another alcoholic male, gave no result. She mated again after several months with the first male and on being killed was found to contain one embryo *in utero* about 2 weeks old.

Female 15, a normal guinea-pig, shows an instructive record. She was mated with an alcoholic male and gave birth to two still-born young.

When mated with another alcoholic male she gave a negative result. Remated with the second male she gave two young, both of which died of convulsions within four weeks after birth. She was then mated with a normal male as a control and gave one vigorous normal offspring which survived.

TABLE 5.—RESULTS OF SUCCESSIVE MATINGS OF TEN FEMALES

Animal	First Mating	Second Mating	Third Mating	Fourth Mating
No. 10 Alc.	Alc. male 4, 1 young died in 6 days	Alc. male 4 0	Alc. male 6 0	Alc. male 4, 1 embryo <i>in</i> <i>utero</i> 2 weeks after
No. 12 Alc.	Alc. male 5 0	Alc. male 5 0	Alc. male 4 0
No. 11 Alc.	Alc. male 6 0	Alc. male 6 0	Alc. male 5; 2 premat. still-born	Alc. male 4 0
No. 13 Nor.	Alc. male 5 1 still-born	Alc. male 5 0	Alc. male 4 0
No. 17 Nor.	Etherized male 1 0	Etherized male 1 0
No. 18 Nor.	Alc. male 5 0	Alc. male 5 0	Alc. male 6 0
No. 7 Nor.	Etherized male 2; 2 premat. still-born	Etherized male 2 0	Etherized male 2 0
No. 14 Nor.	Etherized male 3 0	Etherized male 3 0
No. 19 Nor.	Alc. male 4 0	Alc. male 6; 1 still-born	Alc. male 6 0	Alc. male 5; 4 small, ac- tive, only one-half size, but living
No. 15 Nor.	Alc. male 6; 2 still-born	Alc. male 5 0	Alc. male 5; 2 died fourth week of con- vulsions	Nor. male; 1 normal vigor- ous young

The other records are easily understood.

These experiments have suggested many questions still to be solved, some of which are now being tested, such as the length of time necessary to treat an animal before the resulting offspring is affected, whether this time is equally long for both sexes, and what amount of individual variation may exist. An important point to ascertain is whether the effects of the alcohol treatment are permanent, or does the animal recover after a time and again become capable of giving normal offspring. One of the most valuable problems is to regulate the treatment in such a manner as to induce a definite type of defect with a given kind or degree of treatment. The structure or morphology of the monsters and defective

offspring which occur is to be carefully studied. Many other points might readily be suggested.

Definite and well-controlled experiments with alcohol and other substances on the mammalian offspring have not been sufficiently studied. The work is really in its beginning, and while there is much evidence to show that various toxic agents do affect and modify the offspring, facts are badly needed to demonstrate the regularity and manner of this modification. The present experiments seem to me to prove in a convincing way that alcohol may readily affect the offspring through either parent, and that this effect is almost fatal to the existence of the offspring when the parents have been treated with even fairly large doses of alcohol. Many of the cases seem to indicate further, that the tissues of the nervous system of the offspring are particularly sensitive in their responses to the induced conditions.

My assistant, Miss Craig, has aided me greatly throughout almost the entire progress of these experiments. Last year during my absence abroad she assumed entire control of the animals, and I am indebted to her for this efficient assistance.

SUMMARY

Guinea-pigs have been treated with alcohol in order to test the influence of such treatment on their offspring. Male and female animals are given alcohol by an inhalation method until they begin to show signs of intoxication, though they are never completely intoxicated. They are treated for about an hour at the time, six days per week. The treatment in some of the cases has now extended over a period of nineteen months. The animals may be said to be in a state of chronic alcoholism.

Fifty-five matings of the alcoholized animals have been made, forty-two of which have reached full term and are recorded.

From these forty-two matings only seven young animals have survived, and five of them are unusually small, though their parents were large, vigorous guinea-pigs. The following combinations were made:

1. Alcoholic males were mated to normal females. This is the paternal test, and is the really crucial proof of the influence of alcohol on the germ cells, since the defective offspring in this case must be due to the modified spermatozoa, or male germ cells, from which they arise. Twenty-four matings of this type were made, fourteen of which gave no result or very early abortions; five still-born litters were produced, consisting of eight individuals in all, and five living litters containing twelve young. Seven of these twelve died soon after birth, and only five have survived. Four of the survivors are from one litter and the fifth is the only living member of a litter of three.

2. Normal males were mated with alcoholic females. This is the maternal test. In such cases the alcohol may affect the offspring in two ways—by modifying the germ cells of the mother or acting directly on

the developing embryo *in utero*. Only four such matings were tried. One gave no offspring; three living litters were born, one consisting of three premature young that died at birth, while the other two litters consisted each of one young, which have survived. The alcoholic treatment in one of the last cases was only begun after the mother had been pregnant for about three weeks.

3. Alcoholic males were mated to alcoholic females. This is the most severe test, both parents being alcoholic. Fourteen such matings gave in ten cases no offspring, or very early abortions. Three still-born litters were produced, consisting in all of six individuals, while only one living young was born. *This single offspring from the fourteen matings died in convulsions on the sixth day after birth.*

The young that have died in the experiment showed nervous disorders, many having epileptic-like seizures, and all died in convulsions.

Nine control matings in the same group of animals have given nine living litters, consisting in all of seventeen individuals, all of which have survived and are large, vigorous animals for their ages. Two young from non-alcoholic parents died, but this mother also died two days later. Her diseased condition doubtless affected the suckling young.

Forty-two matings of alcoholic guinea-pigs have given only eighteen young born alive, and of these only seven, five of which are runts, survived for more than a few weeks, while nine control matings have given seventeen young, all of which have survived and are normal, vigorous individuals. These facts convincingly demonstrate the detrimental effects of alcohol on the parental germ cells and the developing offspring.

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PROGRESSIVE INTERSTITIAL HYPERTROPHIC NEURITIS
OF CHILDHOOD OF DEJERINE AND SOTTAS.
REPORT OF A CASE *

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SAN FRANCISCO

This rare disease was first described as an independent affection by Dejerine and Sottas.¹ Previous to their publication Gombault and Mallet² published the account of an observation of a patient having the characteristics of this affection, but they considered it as a case of tabes. There are but three autopsies recorded, those of Dejerine and Sottas,¹ of Dejerine and Thomas³ and the case of Pierre Marie studied by Boveri.⁴

This disease has been studied chiefly in France. The original descriptions of Gombault and Mallet, Dejerine and Sottas and a subsequent publication by Dejerine⁵ give a complete and thorough description of the affection from a pathological as well as a clinical standpoint. A good account is found in the work of Dejerine and Thomas,⁶ and it is briefly considered by Pierre Marie⁷ in his book on neurology. Short accounts are also found in v. Hutinel's System,⁸ in the work of Pfaundler and Schlossmann⁹ and in Osler's Modern Medicine.¹⁰ Sainton¹¹ takes up the question of differential diagnosis and holds very strongly for the independent classification of the affection. This has been brought in question by Marinesco,¹² Beduschi¹³ and Raymond,¹⁴ who believe that the affection is

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1. Dejerine and Sottas: Soc. biol., séance du 18 mars 1893. Mem. Soc. de biol., 5. 9 séries 1893, p. 63.

2. Gombault et Mallet: Un cas de tabès débuté dans l'enfance. Autopsie. Arch. de méd. expér., 1889, p. 385, pl. x.

3. Dejerine and Thomas: Soc. neurol., June 5, 1902. Quoted by Marie in La Pratique Neurologique.

4. Piero Boveri. München. Med. Wchnschr., June 6, 1911, p. 1238.

5. Dejerine: Rev. de méd., November, 1896, xvi.

6. Dejerine and Thomas: Maladies de la Moelle Epinière, Paris, 1909.

7. Marie, Pierre: La Pratique Neurol., Paris, 1911, p. 696.

8. v. Hutinel: Les Maladies des Enfants, Paris, 1909, v, 426.

9. Pfaundler and Schlossmann: Handbuch der Kinderheilkunde, Leipzig, 1910, 4 Band, S. 173.

10. Osler's Modern Medicine: Philadelphia, 1903, vii, 113.

11. Sainton: Thèse de Paris 1889. Quoted by Dejerine, Mal. de la Moelle Ep., p. 776.

12. Marinesco: Arch. de path. exper. et comparée, 1895, quoted by v. Hutinel.

13. Beduschi: Riv. di patholog. nervs. ment., 1906, quoted by v. Hutinel.

14. Raymond: Cliniques, 1903, quoted by v. Hutinel.

identical with, or forms a type of, the myelopathic muscular atrophy type. Charcot-Marie, Dejerine, Sainton, Pierre Marie and Boveri hold for the independence of the affection and claim that the hypertrophy of the nerves, which constitutes one of the most striking characteristics of the disease, is an early pathological finding and not a late development accompanying muscular atrophy and deformity. I believe that the case that I am to report will throw some light on this question.

In Germany, Brach¹⁵ presented two doubtful cases in Berlin in 1903, which he believed to be subforms of this disease. There was, however, no distinct hypertrophy of the peripheral nerves in his cases; and in the discussion which followed Remak thought that they fell rather into the classification of the type of muscular atrophy described by Hoffmann of Heidelberg (progressive neural muscular atrophy).

DESCRIPTION OF DISEASE

It has its commencement in childhood between the eighth and fourteenth year and is frequently a family affection. It is characterized by a progressive course, by ataxia, by muscular atrophy and a marked disturbance of the sensibility together with hypertrophy of the nerve trunks, which is the distinguishing feature of the disease. The muscular atrophy commences in the extremities and the inferior extremity is always involved before the superior. The atrophy of the small muscles of the hands is of the Aran-Duchenne type. The atrophy and the malformation of the feet is such as is met with in Friedreich's ataxia. Fibrillary contractions of the muscles have been occasionally noted. The cutaneous and tendinous reflexes are abolished. The muscular response to the faradic and galvanic currents is diminished; reaction of degeneration is occasionally noted. All forms of sensibility are markedly affected. The walk is that of steppage, but not typically so, as the presence of a certain amount of ataxia produces a very unsteady gait. The sign of Romberg is present and there is a marked ataxia in the finger-nose and heel-knee tests. The reaction of the pupil to light is slowed or entirely absent while the reactions to accommodation and to convergence are conserved. Thus the Argyll Robertson pupil has been observed. The sphincters are intact. The hypertrophy of the nerves is perhaps the most striking feature of the clinical picture. Not only are the great nerve trunks of the extremities involved, but also the cutaneous branches. To quote the description of Dejerine:

It is a uniform hypertrophy without nodosity or any unevenness; the consistency of the nerves is greatly increased and gives to the palpating finger the impression of the arteries of a cadaver previously injected with gelatin. The pressure on the nerve trunks, even though it be great, causes no pain. In the hypertrophic interstitial neuritis there is a veritable analgesia of the nerve trunks to pressure and to the electric current.

15. Brach: Berlin Gesellsch. f. Psychiat. u. Nervenkr., July 13, 1903. Reported in *Neurol. Centrbl.*, 1903, No. 15, p. 748.

Due to the atrophy of the muscles which tend to support the spinal column kyphoscoliosis has been noted. Exophthalmos, scanning speech, intention tremor and nystagmus may be present.

Boveri⁴ has described two clinical types of the affection:

1. *Type Gombault-Dejerine-Sottas*.—Myosis, Argyll Robertson pupils, lightning pains, motor ataxia, fibrillary twitchings, nystagmus, absence of intention tremor, of scanning speech and of exophthalmos and the presence of general muscular atrophy.

2. *Type Pierre Marie*.—No true Romberg, no myosis, no true Argyll Robertson pupils, only slow reaction to light, no lightning pains, motor ataxia, nystagmus or fibrillary twitchings. Intention tremor, scanning speech and exophthalmos present. Muscular atrophy limited to the lower extremity and barely indicated in the hands. This type therefore presents points of similarity to multiple sclerosis.

PATHOLOGICAL ANATOMY (DEJERINE)

The cranial nerves are larger than those of a normal individual, but are far less hypertrophied than the spinal nerves. The sympathetic system takes a prominent part in the hypertrophy. The ganglia of the posterior roots are notably enlarged. The spinal cord is not altered in volume, but there is an atrophy of the posterior columns and an accompanying leptomeningitis in this locality. The dura mater about the cord is not altered. Histologically, the nerves show both interstitial and parenchymatous changes. The interstitial changes are typical. The proliferation of fibrous tissue instead of taking place between the nervous elements in the endoneurium, as in certain other forms of neuritis, takes place about the individual nerve fiber or about several fibers forming an isolating sheath, without, however, the endoneurium being affected. This sheath of connective tissue is disposed concentrically about the nerve fiber much after the fashion of the layers of an onion. In the peripheral nerves one sees few nuclei; on the contrary the spinal roots show abundant nuclei of the embryonic type and vacuoles are numerous. The posterior horns of the gray matter in the cord are small. The cells of the anterior horn studied by Nissl's method show a diminution in number and some are found atrophied and the chromatic network is hardly visible.

DIFFERENTIAL DIAGNOSIS

This affection must be differentiated from the Charcot-Marie type of spinal muscular atrophy, from Friedreich's ataxia, from an ordinary peripheral neuritis and from juvenile tabes. I saw a case in the service of Pierre Marie in Bicetre, which was considered to be a case of Friedreich's ataxia until the discovery of the hypertrophic nerves showed the error in diagnosis. The first described case of this affection was classed as a juvenile tabes. The case I have to report resembles tabes very much in its clinical aspect. The following is the report of the case:

CASE REPORT

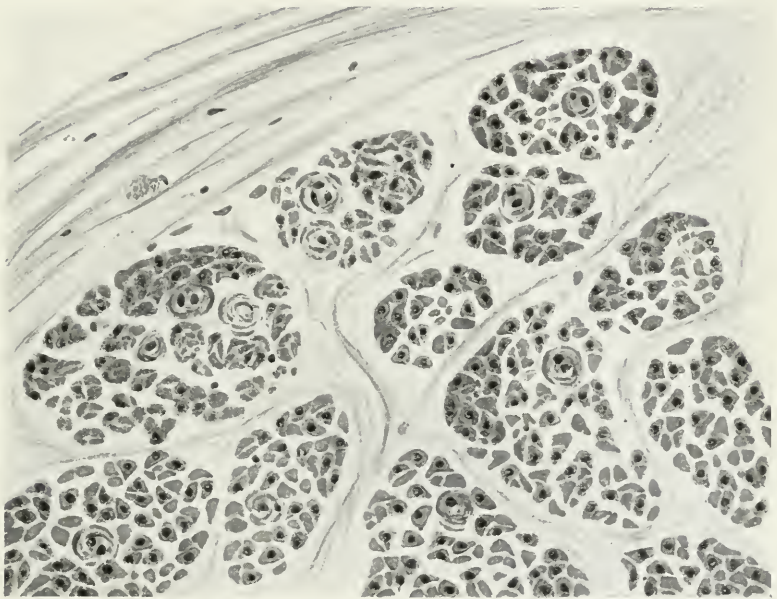
A. B., aged 20, native of San Francisco, of German parentage, newsboy, came to the out-patient clinic in January, 1912, complaining of trouble in walking, and of weakness.

Family History.—Father and mother living and well. The mother gave no history of abortion or miscarriage. The patient has two sisters both of whom are well. An examination of these sisters as well as of the mother presented no evidence of the disease in any one of them. The father was not examined, but he is said to be in good health; and there was no history of a similar affection being present in any branch of the family.

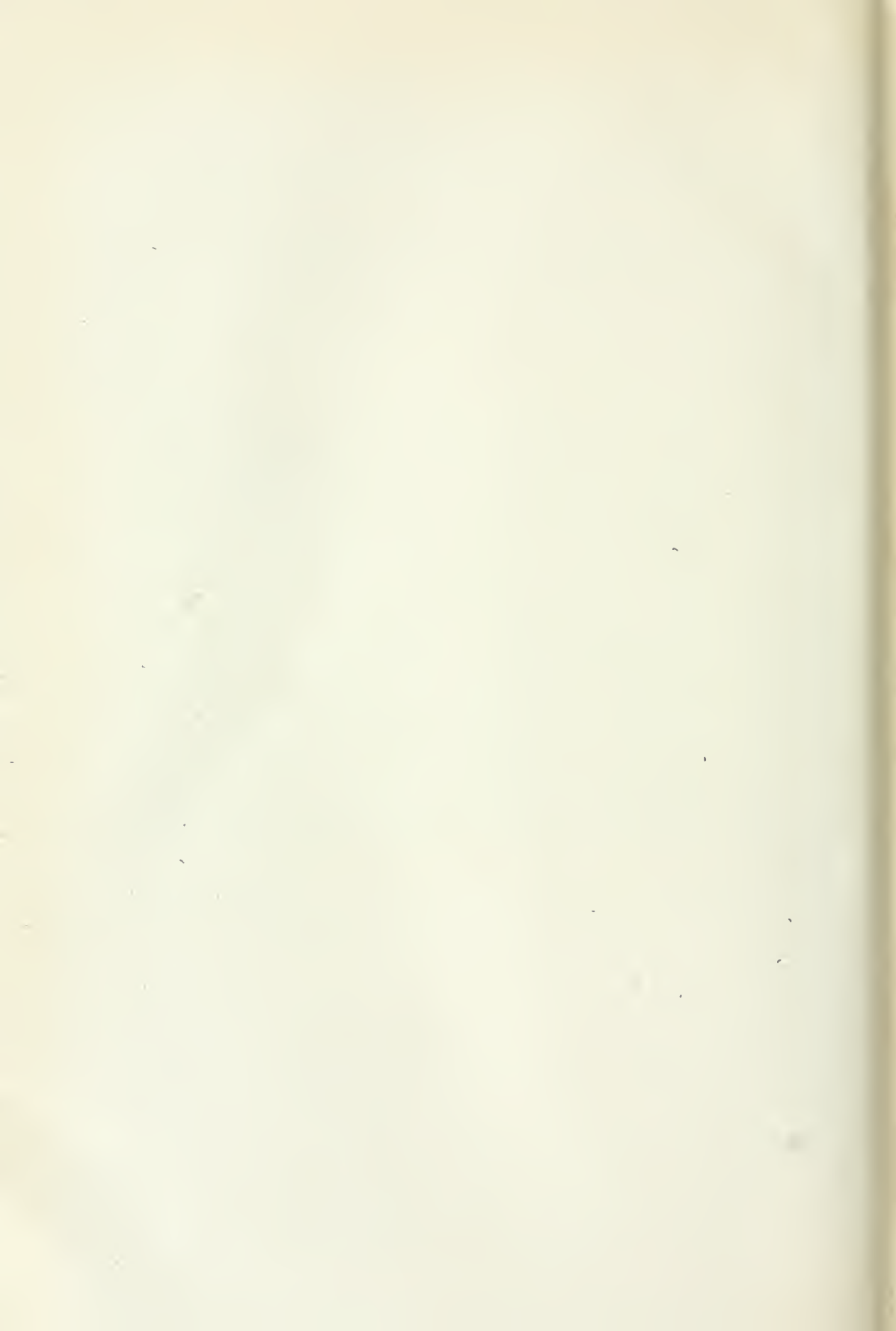
Previous History.—The birth was normal and the infant was normal in every respect. He was fed at the breast for a period of nine months. Dentition commenced at five months, he began walking at 13 months and began to talk at 2 years of age. He had measles, whooping-cough and chicken-pox between the seventh and the ninth years.

Present History.—The present trouble began seven years prior to this report, when he was seized with an attack of general weakness and loss of ambition. The mother thinks the illness commenced from bathing in a contaminated swimming pool. Other children in the vicinity became sick from this same cause she thinks; some took typhoid fever and others had diphtheria. At the onset of his trouble fever was not present and a doctor was not consulted until several months later. At this time failing strength was noticed, which first began in the legs and extended to the arms and hands. This advanced to such a stage that he could not care for himself. There was no trouble with the sphincters. The doctor whom he consulted prescribed a Kneipp water cure. Patient states that while under this treatment he improved slowly for one year. After 1906, the patient's condition remained about the same until September, 1911, since which time the trouble has become worse. The principal complaint of the patient is that the legs feel heavy and get tired easily and that he is unsteady on his feet. He never has had pain. He has difficulty in performing the finer manipulations, such as buttoning his coat and tying his tie. Writing has become difficult and unsteady. There is no disturbance in articulation or deglutition. The sphincters function normally. Sight and hearing are unaffected and the mentality has in no wise suffered. The speech is slow and measured, but the mother states that this has always been so. There is no complaint of headache, vomiting or dizziness. The appetite is good. Constipation is apt to be the rule. The weight has not varied of late; there is no cough or night sweats. Patient leads a very quiet moderate life, living with his parents. Denies all venereal infection and does not use tobacco or indulge in alcohol.

Status, January 26, 1912.—A fairly well nourished young man below the average height. Weight 115½ pounds. Pulse 78, regular and of good volume and tension. The face presents a sallow and rather bloated appearance with puffiness about the eyes. The neck is very broad and thick set. The upper lip is somewhat projected, the labial commissure is transverse and the smile is transverse. There are numerous moles about the face. The spine shows a moderate lateral scoliosis. There are several patches of pityriasis versicolor on the chest. The tongue is hypertrophied, the hypertrophy being of the entire organ and also of the individual papillae; there is a scattered but well-marked exfoliating dermatitis present, shown by numerous slightly elevated patches with a fine sinuous border, forming an incomplete ring. These patches change their position from day to day. No scars suspicious of syphilis are seen on the surface of the body or in the nasopharynx. The tonsils are enlarged. There is no noticeable atrophy of any of the muscles. There is no superficial glandular enlargement. No trembling of the hands. The strength in the hands is diminished. Dynamometer readings: right hand 22 kg., left hand 22 kg. (pressure). The power in the arms, forearms, legs and thighs is fairly well conserved, but the flexors of the foot are decidedly weak while the extensors are not so affected. The walk is that of the steppage gait with at the same time an ataxia and a certain incoordination and swaying. In the pointing movements of the hands and of the feet there is some error when the eyes are open, and this is much increased when the eyes are closed. There



Hypertrophic interstitial neuritis. Transverse section of a superficial nerve of the cervical plexus measuring 3.5 mm. in diameter. Stained by van Gieson's method. The individual nerve fiber is seen surrounded by a sheath of connective tissue consisting of a number of layers disposed concentrically.



is some adiadochokinesis in both hands, but this is not pronounced. There is a distinct Romberg, but no asynergia or "*mouvements démesurés*" (Babinski).

Reflexes: The knee jerks, ankle jerks and radial reflexes are absent. The triceps reflex is present. The abdominal reflexes are present and the plantar reflex is in flexion. The anal and cremasteric reflexes are absent. On percussion of the muscles the muscular reflex is everywhere present.

Sensibility: The sensibility is markedly affected in the extremities but not about the trunk. The sensibility to touch, to heat and cold, and to pain shows a diminution which is more pronounced at the periphery of a member than at its base. The deep sensibility is likewise affected. The pressure sense, sense of position, notion of the position of the segments of a member, including the muscular and articular sensibility, and the osseous sensibility, are impaired. There is a disturbance of the stereognostic sense. Pallesthesia as tested with the Luer fork shows perception of the vibration between 6 and 7 over the lower radius and ulna and 5 plus over the internal malleolus—figures considerably below the normal.

Hypertrophy of the nerves: The nerve trunks of the axilla, the ulnar nerve at the bend of the elbow, superficial branches of the cervical plexus, cutaneous branches on the dorsal surface of the forearms and the external popliteal nerve are markedly hypertrophic and easily palpable. They are not sensitive to pressure and on palpation are found to be free from unevenness and may be rolled under the finger like a sclerotic artery. The ulnar nerve at the bend of the elbow feels about the size of a large goose quill.

Ulnar Nerve Reflex: If the patient be placed in the anatomical position with the palms of the hands anteriorly and the arm be percussed above the olecranon at the inner side, a brusque movement of pronation takes place due to the percussion of the enlarged ulnar nerve and the consequent contraction of the flexor carpi ulnaris. This is found constantly on the left side.

Cranial Nerves: The pupils react well to light and accommodation, are equal in size and regular in contour. The eye movements are normal, there is no contraction of the field of vision and no nystagmus. Report from the eye clinic: "Disks pale in color but normal." Taste and smell are normal. No anesthesia about the distribution of the fifth nerve and no involvement of the facial nerve. Sense of hearing is acute in both ears. The corneal and pharyngeal reflexes are both present. The tongue is not deviated from the mid-line but there is a slight trembling. No trouble in deglutition or articulation.

Electrical Reactions of the Muscles: The electrical reactions of the muscles show an alteration consisting of a hypo-excitability to both the faradic and galvanic currents. In certain muscles an incomplete reaction of degeneration is found. Thus in the extensor communis digitorum and the extensor longus digitorum there is a decided slowing of the contraction to the galvanic current with inversion of the formula: ACC being greater than KCC. In the trapezius, deltoid, biceps, triceps, flexor profundus digitorum, first dorsal interosseus of the hand, biceps femoris, quadriceps femoris, tibialis anticus and flexor longus digitorum there is no inversion but a slight slowing of the contraction, not so marked as in the case of the extensors, where the contraction is almost vermicular.

In the supinator longus, peronei, flexor longus hallucis, extensor proprius hallucis, semimembranosus, semitendinosus, gastrocnemius and soleus the contraction is quick. In every case the faradic excitability is conserved.

An examination of the heart, lungs and abdomen shows normal conditions. The liver is not enlarged and the spleen cannot be palpated. Over the body generally the muscles give a sense of increased tonicity. No fibrillary twitchings of the muscles are observed. The urine shows no albumin nor sugar and a microscopical examination of the sediment shows no casts.

Blood: Red cell count, 4,350,000; white cell count, 4,600. Hemoglobin, 96 per cent.; color index, 89 per cent. Differential white count, polymorphonuclear leukocytes, 58 per cent.; lymphocytes, 40 per cent.; large mononuclear leukocytes, 2 per cent. Wassermann reaction in the blood negative.

Microscopical Examination of an Excised Nerve: One of the enlarged superficial cervical nerves was excised for microscopical examination. This nerve, which was visible beneath the integument, measured 3.5 mm. in diameter in the fresh specimen. Stained sections showed the typical picture of interstitial connective tissue proliferation about the individual nerve fiber. In one place in the specimen, not pictured in the illustration, there is a proliferation of the endoneurium with round-cell infiltration, but this is not characteristic of the general appearance of the specimen. The following is the report of the pathologist, Prof. William Ophüls:

Cross sections through the nerve show a moderate fibrous thickening of the perineurium. There is also in places quite a marked round cell infiltration of the nerve itself with diffuse thickening of the endoneurium. Around many of the nerve fibers the sheath of Henle is thickened which has led to the formation of concentric masses of connective tissue around them. Diagnosis, chronic interstitial hypertrophic neuritis.

TREATMENT

Under arsenic in the form of Fowler's solution in moderate doses and the employment of the constant galvanic current, considerable improvement was obtained. It is probable, however, considering the chronic and progressive character of the disease, that this improvement is only temporary; but its course may extend over many years and the prognosis as far as life is concerned is good.

DISCUSSION

The beginning of the affection in childhood, the marked hypertrophy of the nerves, the ataxia, the loss of muscular strength, the change in character of the electrical muscular reactions, the marked disturbance of the sensibility and the histopathological findings in the hypertrophied nerve fiber itself establishes the diagnosis of this case on a clinical as well as pathological basis. The process is evidently in the early stages, as a number of symptoms such as the atrophy of the muscles, Argyll Robertson pupils and deformity, which may develop at a later stage, are now absent. In this connection I wish to emphasize the early and great hypertrophy of the nerve trunks; for some have held that this occurs only in the later stages of the condition or even go further and believe that in the presence of a marked atrophy the nerve trunks stand out more prominently and are not really hypertrophied, but only apparently so. From our observation of this case this hypertrophy of the nerve trunks which surpasses that seen in two other cases much more advanced, leads us to believe that it plays an important part in the clinical picture, and to hold with Dejerine and others that we have to deal here with a distinct affection.

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THE INFLUENCE OF RADIUM AND OF ITS DECOMPOSITION PRODUCTS ON THE FERMENTS *

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BALTIMORE

Recently radium, its emanations and the products of its decomposition or breaking-down have been coming more and more into consideration as therapeutic agents, not only in skin diseases and diseases with cutaneous manifestations, but also in various "internal diseases" of the most diversified nature, especially carcinoma and the arthritides, and as this interest seems distinctly on the increase and there seems to be a real hope that in some, at least, of these diseases a cure may be obtained by this means, it would seem of interest to know the exact effect of certain salts or products of radium on those substances of such vital importance to the body metabolism — the ferments.

As a slight contribution to this subject we have carried on a series of experiments on the effects of Radium-Lead, Radium D, E and F from radio-active ores, and Radium D, obtained from emanations, on certain of the ferments of the body, choosing as fair examples the proteolytic ferment of the stomach, pepsin, the diastatic ferment of the pancreas and the so-called autolytic ferment of the liver. These experiments have been done *in vitro* and are, of course, open to the criticism which may be applied to all such experiments when one attempts to apply them *in vivo*.

It will be remembered that radium gives off three kinds of rays, α , β and γ , radium itself giving off x -rays and changing into gaseous emanations, these in turn giving off x -rays and changing into Radium A, which changes into Radium B, and this into Radium C, giving off α , β and γ rays; the Radium C changing into Radium D, and this in turn after giving off β and γ rays into Radium E, which finally gives off x -rays and changes into Radium F. Radium itself lasts many years — according to some 1,300 — before this decomposition takes place, the emanations from one to four days, while in Radium A, B and C the

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changes take place very rapidly — in from three to twenty-eight minutes — but much more slowly — in from six to 143 years — in Radium D, E and F. By means of the electroscope we can measure the gaslike radium emanations and determine their amounts in certain units — Mache units. Besides radium, obtained from pitchblende, we have other radio-active substances which will probably find subsequent therapeutic use, such as thorium and actinium.

As to the effects of radium and its decomposition products on the body-tissues, the skin was obviously the first to be studied, and its changes under the influence of radio-active substances are well known: in mild cases we will find redness with swelling and pain, but a return to the normal in about two weeks; in moderate cases, the formation, in addition, of vesicles healing, but with atrophy, in from four to six months, and in severe cases, complete necrosis with ulceration, healing and scar formation being extremely slow.

As regards the effect of radium on other tissues, azoospermia can be produced in animals by exposure to its rays, and also degenerative changes in kidney, spleen, bone-marrow and intestinal follicles, as well as changes, sometimes very grave, in the central nervous system. Bickel and Bergell¹ suggested that the efficacy of many mineral waters might be due to the radium-emanations which they demonstrated in the waters of Wiesbaden and of other spas, this probably explaining the much less marked effects produced by the bottled waters than by those drunk directly from the source, as the emanations are rapidly lost, according to these observers, in forty-eight hours at the longest. They also showed that the radio-active Wiesbaden-Kochbrunnen activates the peptic ferment of the stomach, and thus counteracts the inhibiting effect of the salts themselves, as shown by Schmidt, Pfeiffer, Walberg and others, in the case of certain mineral waters which have lost their radium-emanations by standing. Rodari, however, showed that radium-emanations have no especial influence on the hydrochloric acid of the gastric juice.

In our series of experiments we have studied the influence on pepsin, pancreatic diastase and the antolytic ferment of the liver of the following substances: (1) Radium-Lead powder; (2) radio-active ores shaken up with water and with lead chlorid ($PbCl_2$) in solution in excess, one containing Radium D with a very small amount of Radium E, and being very slightly radio-active, the other, containing Radium D, E and F, being very radio-active, while in our third group of experiments we used Radium D obtained from radium-emanations; 4,800 c.c. of ordinary tap water impregnated with 50,000 Mache units being evaporated to about

1. Bickel and Bergell: *Ztschr. f. klin. Med.*, 1905, lviii, and *Verhandl. d. Congress f. inn. Med.*, xxii, 157.

250 c.c., radio-activity now being but 0.3 Mache units per c.c.; i. e., seventy-five in all.

As to the methods employed for the quantitative determination of the pepsin and diastase, but a few words are necessary. For *pepsin*, we used the *edestin* method, putting into each of a row of tubes 2 c.c. of a 0.1 per cent. solution, made with hydrochloric acid of the acidity of 30 (decinormal HCl 30 c.c., distilled water 70 c.c.), to each of which row of tubes we had previously added fresh gastric juice (from the dog) in decreasing amounts, 0.5 c.c. in the first, 0.25 c.c. in the second, 0.125 c.c. in the third, etc., bringing up the amount of the fluid in each tube to 1 c.c. with hydrochloric acid of acidity equal to 30, as at this degree, of acidity the peptic action seems to be at its optimum. To each of the tubes we then added a certain number of cubic centimeters, three or five of the solution to be tested; to another row of tubes of the same number of cubic centimeters of the control-fluid, distilled water, or evaporated tap water as the case might be; the tubes were tightly corked, kept in the thermostat at 37.5 C. for twenty-four hours, and then tested with a few cubic centimeters of saturated sodium chlorid (NaCl) solution, to determine by the white precipitate formed in which tubes edestin still remained undigested. The limit of digestion was expressed in units; i. e., the number of cubic centimeters of 0.1 per cent. edestin solution which would be completely digested by 1 c.c. of pure gastric juice.

The diastase was determined by the Wohlgemuth method, 5 c.c. of a 1 per cent. starch solution being placed in each of the row of tubes with pancreatic juice in decreasing amounts, and after the addition of a certain amount of the substance to be tested or of the control-fluid, and 1 c.c. of toluol to each tube to inhibit bacterial action, the tubes were tightly corked, kept in the thermostat for twenty-four, forty-eight, seventy-two or ninety-six hours, and then tested with decinormal iodine solution. The digestive power of the juice was again expressed in units; i. e., the number of cubic centimeters of 1 per cent. starch solution which would be completely digested by 1 c.c. of pure pancreatic juice. In these experiments the gastric juice was obtained absolutely fresh each time from a dog with a Pawlow stomach, while the pancreatic juice, of which we used two specimens from two dogs, had been obtained a little while before from dogs with operative pancreatic fistulas, and, after the addition of toluol, kept in flasks tightly corked in the ice-chest until needed.

Before describing the method used for the estimation of the splitting produced by the *autolytic ferment* of the *liver*, it might be of interest to say a few words about this ferment.

The numerous activities of that organ, so important in the intermediary metabolism—the liver—are intimately connected with ferments; although we have not found as yet the ferment for every metabolic

process in this organ, nevertheless it is highly probable that it is present. Among the ferments already found in the liver may be mentioned a ferment which splits polypeptids, arginase which acts in the formation of urea, a nuclease, a diastase, a glycolytic ferment, several oxydases, a katalase, a lipase and an enterase; according to Jacoby these ferments are not each in its special type of cell, but the colloid ferment-molecules are in one and the same cell, although definitely separated from each other.

In comparison with the close relationship existing between the liver and the metabolism of the carbohydrates, that between this organ and the proteid metabolism is comparatively loose, although it is *not* probable that the entire protein synthesis has taken place during the passage of the amino-acids through the intestine wall, but probably a part goes through unchanged into the circulation and is synthetized in the liver and other organs. In 1876 Salkowski² brought forward the view that the splitting of the protein in the organs during life is caused by intracellular ferments, the purin bases being split off from the nucleoproteins and nucleinic acids.³ According to Neumeister and Jacoby there is no doubt at present of the constancy of these autolytic appearances dependent on intracellular ferments, probably specific in character. Salkowski⁴ found that if fresh liver is finely cut up and chloroform water added to prevent bacterial decomposition, protein digestion takes place in considerable amount. In aseptic autolysis, Magnus-Levy⁵ found lactic acid, acetic acid, butyric acid and carbon-dioxid gas. The question whether the autolytic processes are to be regarded as post-mortem phenomena or whether it can be assumed that they play a rôle during life is still under discussion, but the great weight of opinion is in favor of the latter view, i. e., that protein can be broken down in the liver during life into its separate constituents.

The method employed by us to determine quantitatively the extent of this *autolysis* was practically the same as that used by Salkowski and was as follows: Thirty grams of very finely hacked fresh dog's liver was put into a series of flasks, into each of which 50 c.c. of the fluid to be tested or of the control-fluid with 0.5 c.c. pure chloroform (or a certain weight of substance, if a solid was used), and then enough freshly and carefully made 1 per cent. chloroform-water added to make the total amount of fluid in each flask 300 c.c. After being well shaken the flasks were tightly corked, made air-tight with paraffin and placed in the thermostat at 37.5 C. At the end of twenty-four and forty-eight hours, 50 c.c. of the supernatant fluid was pipetted off from each, the corks replaced and the flasks again made air-tight, while at the end of seventy-two hours in certain experiments, ninety-six hours in others, 50 c.c. of the fluid

2. Salkowski: Ber. d. deutsch. chem. Gesellsch., 1896, 719.

3. Salkowski: Ztschr. f. klin. Med., 1891, xvii, Suppl. p. 79.

4. Salkowski: Festschr. f. Leyden, 1891.

5. Magnus-Levy: Beitr. z. chem. Phys. u. Path. (Hoffmeister), 1902, ii, 261.

was filtered off, as the experiment was then at an end. The 50 c.c. of fluid was treated as follows: One gram of potassium phosphate (K_3PO_4) was added, the fluid was boiled for three minutes and then filtered, and enough distilled water added to the filtrate to bring it up to 50 c.c.; from 10 c.c. of this the nitrogen was determined by the Kjeldahl method. If the portions of 50 c.c. each in the same experiment are put in small flasks of exactly the same size and shape, kept in boiling water in the water-bath for exactly the same length of time (five minutes, for example) and filtered through filter papers and funnels of precisely the same dimensions, it will not be necessary to bring up the last filtrate to 50 c.c. with distilled water, and a slight source of possible error will be eliminated.

EXPERIMENTS

Our experiments were made as follows:

A. With Radium-Lead—

Autolytic Experiments.—Two control experiments, two experiments with .00465 gr. Radium-Lead in each flask, 1 with .0093 gr. Radium-Lead twenty-four, forty-eight and ninety-six hours.

B. With Radium D (E) and Radium D, E, F, obtained by shaking up radio-active ores with water, with lead chlorid ($PbCl_2$) in excess.

1. *Autolytic Experiments.*—One control with distilled water (50 c.c.) one experiment with saturated $PbCl_2$ solution (50 c.c.); two with the very slightly radio-active Radium D (E) (50 c.c.); two with markedly radio-active Radium D, E, F (50 c.c.), twenty-four, forty-eight and seventy-two hours.

2. *Diastase Experiments.*—One series of twenty-four hours with 5 c.c. of distilled water, saturated $PbCl_2$ solution, Radium D (E) and Radium D, E, F; two series of forty-eight hours, and one of ninety-six hours.

3. *Pepsin Experiments.*—One series with 5 c.c. of distilled water, saturated $PbCl_2$ solution, Radium D (E) and Radium D, E, F; one series—the same without the distilled water control; one series—the same as the first but with 3 c.c. of fluid in each tube.

C. With Radium D, obtained by evaporating 4,800 c.c. of ordinary tap water impregnated with 50,000 Mache units of radium emanations to about 250 c.c., the radio-activity by this being reduced to 75 Mache units in the entire quantity of fluid, and as control 4,800 c.c. of ordinary tap water evaporated to about 300 c.c. (radio-activity=0).

1. *Autolytic Experiments.*—Control (50 c.c.), one experiment with Radium D (50 c.c.); one control and one experiment using only 12 gm. of liver in each flask, 50 c.c. of control water and Radium D water and chloroform water to 120 c.c.

2. *Diastase Experiments.*—One series of twenty-four hours, two of forty-eight hours, and two of ninety-six hours with 5 c.c. of Radium D and control-water; one series of forty-eight, one of seventy-two and one of ninety-six hours with 3 c.c.; one series of twenty-four and one of forty-eight hours, with 5 c.c. of distilled water, unfiltered control-water and filtered control-water.

3. *Pepsin Experiments.*—One series with 5 c.c. of Radium D and of the control-water.

A consideration of the figures and the appended tables will justify us in drawing the following conclusions:

In regard to the *autolytic ferment* of the liver, none of the substances used, Radium-Lead, Radium D (E) and Radium D, E, F, from radio-active ores or Radium D from the emanations, had any effect whatever, the figures of the experiments and of the control being practically identical; the higher figures with lead chlorid solution than with distilled water suggest that this salt may have a distinctly activating effect on autolysis, and we hope subsequently to study more thoroughly the influences of this and other salts of the heavy metals on this most interesting type of ferment action.

As regards the *diastatic ferment*, with Radium D (E) and Radium D, E, F from radio-active ores, the former — very slightly radio-active — had practically the same effect as the control — the saturated solution of lead chlorid, while the very radio-active Radium D, E, F had a marked inhibiting effect; in all these fluids with lead chlorid in solution in excess, the ferment-action was distinctly inhibited as compared to the action of distilled water. With Radium D obtained from the emanations compared to evaporated tap water (markedly alkaline in this case), each containing considerable sediment and quite a large amount of salts, as in each case 4,800 c.c. of ordinary tap water was evaporated to about 300 c.c., most of the experiments showed that the Radium D obtained in this way had a stimulating effect on the diastase, this being more marked the longer the tubes were allowed to remain in the thermostat and the greater the amount of fluid used. A comparison between the evaporated water, rich in salts and sediment, and distilled water showed that the former had a markedly stimulating effect on diastase, this activation being due to the salts in solution and not to the sediment.

As regards *pepsin*, with respect to Radium D (E) and Radium D, E, F each, of course, with lead chlorid present in excess, the radium preparations showed a slight inhibiting effect as compared to the saturated lead chlorid solution, this being more marked with the very radio-active Radium D, E, F; a comparison between distilled water and saturated lead chlorid solution showed that the latter had a marked inhibiting effect on pepsin, just the opposite of its effect on autolysis. The results with Radium D obtained from the emanations were inconclusive, due to the lack of material, but the one experiment performed seemed to suggest that the effect was slightly inhibitory.

RECAPITULATION

Thus, to recapitulate, none of the radium preparations used seemed to have any effect on the *autolytic ferment* of the liver, although saturated lead chlorid solution appeared to activate it; with diastase the very radio-active Radium D, E, F possessed an inhibiting effect, while the Radium D

from emanations had a stimulating effect, this increasing with the length of time and the amount of fluid used, while this ferment is also markedly activated by the salts in evaporated tap water; with *pepsin* we found a slight inhibiting effect, more marked with the very radio-active Radium D, E, F, although slight in comparison with the inhibiting effect of saturated lead chlorid solution.

The detailed figures of the experiments follow.

TABLES FOR THE ACTION OF RADIUM AND ITS DECOMPOSITION PRODUCTS ON THE FERMENTS (AUTOLYTIC FERMENT OF LIVER, DIASTASE, PEPSIN)

A. Experiments with the Autolytic Ferment of the Liver

First Series of Experiments with Radium-Lead (Radium-Blei)

Liver, Chloroform-Water			
	gm.	c.c.	
I.	30	300	(Control)
II.	30	300	(Control)
III.	30	300	.00465 gm. Radium-Lead
IV.	30	300	.00465 gm. Radium-Lead
V.	30	300	.0093 gm. Radium-Lead

Results (Expressed Both in c.c. of N/10 NaOH and in Nitrogen)

After 24 Hours			After 48 Hours			After 96 Hours		
I.	3.46 c.c.	(.004858 gm.)	6.33 c.c.	(.008887 gm.)	9.03 c.c.	(.012678 gm.)		
II.	3.25 c.c.	(.004565 gm.)	6.51 c.c.	(.009140 gm.)	8.93 c.c.	(.012538 gm.)		
III.	3.43 c.c.	(.004818 gm.)	5.83 c.c.	(.008185 gm.)	8.33 c.c.	(.011696 gm.)		
IV.	3.13 c.c.	(.004397 gm.)	6.7 c.c.	(.009407 gm.)	9.24 c.c.	(.012973 gm.)		
V.	3.12 c.c.	(.004380 gm.)	6.44 c.c.	(.009042 gm.)	9.2 c.c.	(.012917 gm.)		

Second Series of Experiments with Radium D (E) and Radium D, E, F, Obtained from Radio-Active Ores with Lead Chlorid (PbCl_2) in Solution in Excess

Liver, Chloroform-Water			
	gm.	c.c.	
I.	30	300	(Control)
II.	30	250	.50 c.c. sat. Pb. Cl_2 sol. .5 c.c. CHCl_3
III.	30	250	.50 c.c. Radium D (E) sol. .5 c.c. CHCl_3
IV.	30	250	.50 c.c. Radium D (E) sol. .5 c.c. CHCl_3
V.	30	250	.50 c.c. Radium D, E, F, sol. .5 c.c. CHCl_3
VI.	30	250	.50 c.c. Radium D, E, F, sol. .5 c.c. CHCl_3

Results (Expressed Both in c.c. of N/10 NaOH and in Nitrogen)

After 24 Hours			After 48 Hours			After 72 Hours		
I.	7.2 c.c.	(.01008 gm.)	8.24 c.c.	(.01154 gm.)	10.82 c.c.	(.01515 gm.)		
II.	10.7 c.c.	(.01498 gm.)	12.4 c.c.	(.01736 gm.)	15.7 c.c.	(.02198 gm.)		
III.	11.3 c.c.	(.01582 gm.)	13.9 c.c.	(.01946 gm.)	16.0 c.c.	(.02240 gm.)		
IV.	11.4 c.c.	(.01596 gm.)	12.9 c.c.	(.01806 gm.)	15.6 c.c.	(.02184 gm.)		
V.	10.9 c.c.	(.01526 gm.)	12.2 c.c.	(.01708 gm.)	15.7 c.c.	(.02198 gm.)		
VI.	10.6 c.c.	(.01484 gm.)	12.6 c.c.	(.01764 gm.)	16.4 c.c.	(.02296 gm.)		

Third Series of Experiments with Radium D Obtained from Emanations

Control Water 4800 c.c. of ordinary (tap) water evaporated to (about) 300 c.c.; radio-activity = 0.

Radium D Water 4800 c.c. of ordinary (tap) water with 50,000 Mache units evaporated to 250 c.c. Radio-activity of 1 c.c. (after evaporation)=3 Mache unit, i. e., 75 Mache units in the 250 c.c.

	Liver gm.		Chloroform Water, c.c.
I.	12	Control Water 50 c.c. CHCl ₃ .5 c.c.	70
II.	30	Control Water 50 c.c. CHCl ₃ .5 c.c.	250
III.	12	Radium D Water 50 c.c. CHCl ₃ .5 c.c.	70
IV.	30	Radium D Water 50 c.c. CHCl ₃ .5 c.c.	250

Results (Expressed Both in c.c. of N/10 NaOH and in Nitrogen)

	After 24 Hours	After 48 Hours	After 72 Hours
I. 4.95 c.c. (.00693 gm.)			9.95 c.c. (.01393 gm.)
II. 5.4 c.c. (.00756 gm.)		8.59 c.c. (.01203 gm.)	10.8 c.c. (.01512 gm.)
III. 4.98 c.c. (.00697 gm.)			10.28 c.c. (.01439 gm.)
IV. 5.1 c.c. (.00714 gm.)		7.9 c.c. (.01106 gm.)	11.2 c.c. (.01568 gm.)

B. Experiments with Diastase

Second Series of Experiments with Radium D (E) and Radium D, E, F, Obtained from Radio-Active Ores with Lead Chlorid (Pb Cl₂) in Solution in Excess

(a)	Substance Used	Diastase in Starch Units		
		In 24 Hours	In 48 Hours	In 96 Hours
	5 c.c. distilled H ₂ O	2560	2560	2560
	5 c.c. Pb Cl ₂ solution (Sat.)	1280	1280	1280
	5 c.c. Radium D (E) water	1280	1280	1280
	5 c.c. Radium D, E, F, water	320	320	320
(b)	5 c.c. distilled water		1280
	5 c.c. Pb Cl ₂ solution (Sat.)		640
	5 c.c. Radium D (E) water		640
	5 c.c. Radium D, E, F, water		80	160

Second Series of Experiments with Radium D Obtained from Emanations (See Under Autolytic Experiments)

(a)	Substance Used	Diastase in Starch Units			
		In 24 Hours	In 48 Hours	In 72 Hours	In 96 Hours
	5 c.c. shaken, evaporated water	2560	2560	2560
	5 c.c. shaken Radium D water	3840	5120	10240
(b)	5 c.c. shaken, evaporated water	2560	2560
	5 c.c. shaken Radium D water	5120	10240
(c)	3 c.c. shaken evaporated water	1920	1920	2560
	3 c.c. shaken Radium D water	2560	2560	2560
	3 c.c. distilled water	640	640	640
(d)	5 c.c. shaken evaporated water	2560	2560
	5 c.c. filtered evaporated water	2560	2560
	5 c.c. distilled water	640	640

C. Experiments with Pepsin

First Series of Experiments with Radium D (E) and Radium D, E, F, Obtained from Radio-Active Ores with Lead Chlorid (Pb Cl₂) in Solution in Excess

(a)	Substance Used	Pepsin in Edestin Units	
		24 Hours	in Thermostat
	5 c.c. distilled water	64,000	
	5 c.c. Pb Cl ₂ solution (sat.)	12,000	
	5 c.c. Radium D (E) water	8,000	
	5 c.c. Radium D, E, F, water	4,000	

	Substance Used	Pepsin in Edestin Units After 24 Hours in Thermostat
(b)	5 c.c. Pb Cl ₂ solution (sat.)	12,000
	5 c.c. Radium D (E) water	4,000
	5 c.c. Radium D, E, F, water.....	3,000
(c)	3 c.c. distilled water	32,000
	3 c.c. Pb Cl ₂ solution (sat.)	12,000
	3 c.c. Radium D (E) water	8,000
	3 c.c. Radium D, E, F, water.....	8,000

Second Series of Experiments with Radium D from Emanations (See Autolytic Experiments)

Substance Used	Pepsin in Edestin Units After 24 Hours in Thermostat
5 c.c. shaken evaporated water	8,000
5 c.c. shaken Radium D water.....	6,000

PATHOLOGICAL DEVIATIONS IN THE CHEMISTRY OF UREMIC BLOOD *

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The two theories of uremia that claim most attention at the present time are the toxemic and what may be called terminal state—the idea that this condition is not a pathological unity at all but a final dissolution. The latter conception is founded more on the failures of research to elucidate a specific etiological factor than on the lack of a clear-cut clinical picture. Since this idea cannot be tested by investigation, it demands no special consideration. The hypothesis that uremia is a toxic state, however, has much in its favor by way of analogy, and has become more or less rooted in our minds because of the men who have sanctioned this theory in one form or another.

As to the nature of the toxic agent, the ideas advanced may be subdivided under two heads, depending on whether the toxic material is supposed to be a normal catabolic product retained in the body through renal failure to eliminate it, or whether this toxic substance is conceived to be the product of a perverted metabolism incident to renal deficiency. The earlier investigators naturally advanced the “retention” theory. Babington, working with a case of uremia under the care of Bright, and Christison, both noted the abnormally high urea content in the blood and attached peculiar significance thereto. Likewise other substances known to occur in urine, creatinin, uric acid, etc., when found in the blood in uremia, were called on to account for the uremic syndrome.

In his conceptions Frerichs departed from the traditional ideas, inasmuch as he believed, not the urea itself, but a substance formed from urea through ferment action, to be the cause of symptoms. This was the first suggestion made that the cause of uremic intoxication depended not on retained excretory substances, but on a product of perverted metabolism. Nearly all of the later investigations on uremia, with the exception possibly of that of Bouehard, have been directed toward the discovery of some product of abnormal metabolism which might account for the nervous manifestations found in uremia. Estimations of “retention” nitrogen and deductions therefrom have been confined in the main to the realm of diagnosis and prognosis.

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Since the toxemic theory of uremia rests at present on no demonstrated facts, it seems desirable to examine the changes found in the blood with a view of ascertaining, in the first place, in how far these deviations from normal are explicable by pure renal failure; and, secondly, any evidence of disordered metabolism.

From the chemical point of view, blood plasma may be regarded as a solution of various crystalloids holding in suspension a number of colloids. The latter are various protein, lipoid and carbohydrate substances, while the crystalloids consist of both inorganic and organic substances. Relative to these organic crystalloids it has been repeatedly shown that with some of them at least there is a quantitative increase in the majority of uremic bloods. Qualitative deviations from the normal have been claimed by some investigators, but are not accepted as conclusive for technical reasons. If it were a demonstrated fact, however, that in uremic blood there exists some qualitative change in the content of organic, non-protein compounds, this fact would be of weight in showing an abnormal cellular metabolism. With purely quantitative changes, however, the interpretation would be more difficult. Likewise decided changes in the colloids, or the presence of an abnormal colloidal substance, could hardly be regarded in any light other than fundamentally metabolic. Since any fact that could be demonstrated relative to abnormal proteins might be conclusive, this point was investigated first, although demonstration seems almost impossible in the present state of our knowledge.¹

The chaotic state of knowledge relative to the proteins in blood is dependent primarily on the fact that there is no unanimity of opinion among chemists as to methods. In the first place, sufficient attention has not been accorded to the collection of samples for analysis. Defibrinated blood (plasma), serum and unclotted, centrifugalized blood have been indifferently used, with corresponding discordant results.² Even when the same materials have been employed results differed.

That data obtained by using serum expressed from clotted blood can give no idea of actual conditions in circulating blood, has been pointed out by Porges and Spiro.³ In the separation of globulin from albumin, two methods have been commonly employed: saturation with magnesium sulphate as advised by Hammarsten and Hoffman, and half saturation with ammonium sulphate. As to the relative merits of these two procedures there are two general opinions. Against magnesium sulphate it has been asserted that this salt precipitates not only globulin, but a fraction of the albumin also.⁴

1. See papers of E. Freud and E. Abderhalden relative to albumose in dog blood. *Biochem. Ztschr.*, 1908, vii, viii, ix, x and xi.

2. Hoffman: *Arch. f. p. Path. u. Pharm.*, 1883, xvi, 183.

3. Porges and Spiro: *Beitr. z. chem. Physiol. u. Path.*, 1902, iii, 277.

4. Heynsius: *Arch. f. d. ges. Physiol.*, 1884, xxxiv, 330; Marcus: *Ztschr. f. physiol. Chem.*, 1889, xxviii, 559.

On the other hand, objections have been made to the use of ammonium sulphate as a reagent. Wiener contends that other proteins than globulin are thrown down by half saturation unless the serum be much diluted.⁵ It appears that if the serum be successively diluted and half saturated with ammonium sulphate, less protein is precipitated than when undiluted serum is used. This difference may amount to 20 per cent. Haslam⁶ believes that one-half saturation with ammonium sulphate does not remove all of the globulin from serum, since further saturation effects the precipitation of a protein substance, which on dissolving in water, is precipitated by half saturation. This phenomenon is strongly suggestive of "denaturation." Even less than half saturation of serum with ammonium sulphate is sufficient to precipitate completely all globulins in the opinion of Kander.⁷ In view of this disparity of opinion regarding a simple separation, it would seem a hopeless undertaking to demonstrate the presence or absence of any protein substance that serum may contain, and in this paper no claim is made for the individuality of such substances. That question has been avoided, to some degree at least, as the results are comparative. Normal bloods were subjected to the same procedures as pathological bloods, and in some cases differences in behavior are recorded.

TECHNIC

Since some of the proteins in blood are rendered insoluble in water after contact with alcohol this fact was utilized as the first step in the method; 200 c.c. of citrated blood were thoroughly mixed by shaking with 600 c.c. of alcohol (95 per cent., redistilled with calcium hydrate). After standing for twenty-four hours the alcoholic liquid was filtered off with a suction pump, leaving a granular material in the filter. This precipitate was then suspended in 400 c.c. of distilled water, thoroughly mixed with toluol as a preservative, let stand in a stoppered flask for twenty-four hours, at the end of which time the extract was filtered off and the slightly reddish, translucent filtrate collected. The filtrate contained considerable protein which was in part removed by bringing the liquid to a boil and filtering. This last filtrate was saturated while still warm with ammonium sulphate, which caused a further precipitation of protein-like flakes. After standing for twenty-four hours the protein and some excess of ammonium sulphate were removed by filtration⁸ and the filtrate freed from the precipitating agent by means of barium carbonate. The final filtrate after this procedure was water-clear and this was evaporated to a small volume (about 25 c.c.) on the water-bath.

This method was carried out on two samples of normal human blood, and three samples of blood from uremic patients.

In the case of two of the uremic bloods the final filtrate gave faint but distinct biuret reactions. An endeavor was then made to precipitate any protein still in solution by adding 500 c.c. of absolute alcohol. At first no change was notable but in the course of an hour the material had taken on a milky appearance and by

5. Wiener: *Ztschr. f. physiol. Chem.*, 1911, xxxiv, 29.

6. Haslam: *Jour. f. Physiol.*, 1904, xxxii, 267.

7. Kander: *Arch. f. exper. Path. u. Pharm.*, 1886, xx, 411.

8. Much more of the excess of ammonium sulphate might have been precipitated with alcohol at this point, and the concentration of liberated ammonia considerably reduced, although it is unlikely that the evolved ammonia had any material effect on the products.

the next day a small amount of white precipitate collected on the bottom of the beaker leaving a clear fluid. This precipitate was filtered off and redissolved in water.

The watery solution gave the following reactions: Potassium mercuric iodid and hydrochloric acid caused a turbidity, as did also phosphotungstic acid and Millon's reagent. Tannic acid gave a small amount of slightly brownish precipitate. The Hopkins-Cole reaction was negative. Trichloroacetic, chromic and phosphomolybdic acids failed to cause change. These reactions were concordant with two samples of uremic blood. With the third sample and with two normal bloods there was no precipitation whatever with absolute alcohol.

An attempt was made with other samples to rid the solutions of ammonium sulphate by dialysis, but it was found that the substance in question was lost in this way. That the substance is readily diffusible was demonstrated on a small portion of the alcohol precipitate. After twenty-four hours' dialysis in a collodion sack, nothing could be recovered.

In addition to the investigation of human bloods, dog blood was studied; one normal and one sample from a dog whose renal arteries had been ligated forty-eight hours before the sample was collected. Both samples failed to yield any protein-like substance after the above treatment.

The results above recorded are not conclusive as to presence of a peculiar protein in uremic blood, and by the methods now known any result could not escape the criticism that the protein substance recovered might have been produced in the process of isolation.

NON-COLLOIDAL NITROGEN

The consideration accorded to the non-colloidal nitrogen in uremic blood has been mainly from the clinical aspect, although it should be possible, provided suitable methods are employed, to disclose a deeper significance in the relative distribution of the nitrogen fractions. The method that has been most used in the past for the separation of the blood proteins as a preliminary to determining the "filtrate" nitrogen is that of precipitation by means of alcohol. This method was employed in a preliminary series in order to learn something of the nature of the fractions composing the total alcohol-soluble nitrogen. The technic was to precipitate the proteins of blood by the addition of four volumes of alcohol. Aliquot parts of this filtrate were used for the separate determinations.

The results of analyses recorded in Table 1 require perhaps a word of comment as to their clinical moment. It has been quite positively asserted and with equal conviction denied that the "filtrate" nitrogen is significant, both in diagnosis and prognosis. A glance at Table 1 indicates that, in general, there is a very considerable increase in the amount of

"filtrate" nitrogen in the nephritis patients who are sufficiently sick to seek hospital aid. This, however, is not an invariable rule, and is not to be regarded as pathognomonic, since there are exceptions wherein very severe cases show an approximately normal figure for the "filtrate" nitrogen. Conversely, it has been observed that high "filtrate" nitrogen occurs with other diseases than nephritis, for example, some valvular cases and pneumonia. This does not vitiate all value, but indicates that the results must be interpreted in the light of the whole clinical picture.

TABLE 1.—SHOWING ALCOHOL-SOLUBLE NITROGEN AND UREA NITROGEN IN VARIOUS CONDITIONS

Case Number	Date 1910	Diagnosis	Alcohol-Soluble N, g. per L.	Urea N, g. per L.	Discharged
20,488	Oct. 4	Chronic nephritis	0.90	0.84	
20,488	Oct. 12	Chr. nephritis uremia	1.49	0.72	
20,488	Oct. 22	Chr. nephritis uremia	2.17	1.71	Death Oct. 23
20,488	Oct. 22	Chr. nephritis uremia	1.70	Spinal fluid
20,144	Chr. nephritis uremia	3.93	1.40	Death
P. P.	Nov. 10	Uremia	3.61	1.72	Death
20,684	Dec. 1	Chronic nephritis	1.64	1.19	
20,684	Dec. 4	Chro. nephritis uremia	2.14	1.78	Death
20,697	Dec. 8	Chro. nephritis uremia	1.17	0.74	Discharged improved
St. L. II.	1911	Chro. nephritis uremia	0.53	0.28	Death
17,524	Jan. 20	HgCl ₂ poison	1.45	0.88	Death
17,524	Jan. 18	Aneurysm, nephritis	0.52	0.24	Discharged improved
20,650	Jan. 18	Chronic nephritis	0.43	0.27	Discharged improved
20,746	Uremia	1.06	0.68	Discharged improved
20,193	Chronic nephritis	1.23	0.66	Death
20,108	Chronic nephritis, cerebral hemorrhage	0.89	0.23	Discharged improved
KIDNEYS, NORMAL					
20,514	Chr. valvular disease cerebral embolism	0.42	0.20
20,511	Gastric ulcer	0.54	0.39
R. W. C.	Epilepsy	0.33
R. W. C.	Gas poison	0.76	0.41
O. P. D.	Gastritis	0.53	0.29

As to prognosis, the results of analyses in Table 1 at first glance do not appear equivocal. There was, in those cases in which more than one examination was possible, a heaping up of catabolic products as death approached which amounted to an enormous increase over the normal blood content. But that only one analysis gives little information as to the immediate outcome of the case unless the "filtrate" nitrogen is very high, is shown by the results for those cases in which the patient did well notwithstanding the evidence of retention. And one case is of record in

which typical uremia resulted in death although the blood analysis would have indicated an excellent prognosis. When the total alcohol-soluble nitrogen is 1 gm., or over 1 gm. per liter, the prognosis is probably to be regarded as extremely grave, since of eight such cases five terminated fatally. But in order to interpret laboratory results of this nature with accuracy it is necessary to estimate with a greater degree of nicety than we are now able, the efficiency of the heart muscle. It is, in many cases of uremia, by no means easy to determine whether death is due primarily to a toxemia or to a failure of the circulation. There are cases in which the toxic element in the clinical picture is predominant; in others the uremic state is overshadowed by evidences of cardiac incompetence; then the third class in which both factors are detectable, but an evaluation of their relative importance in causing death is most difficult. It is possible that the cardiac element is the explanation of the fatal issue in some of the cases in which "retention" nitrogen is not very much above normal.

The percentage of the alcohol-soluble nitrogen that is found as urea nitrogen is extremely variable and seems to bear no constant relation to the total alcohol-soluble nitrogen. The urea nitrogen may constitute as much as 90 per cent. of this total nitrogen, or be only about 36 per cent. of it. What substances contain the remainder of the nitrogen has been determined only in part. In but a few instances was there sufficient material available for searching analyses. It was found that on evaporation of the alcohol from a portion of the alcohol filtrate the residue has a fatty consistency and it was conjectured that lecithin⁹ or some other nitrogenized fat would be detectable. A specimen of uremic blood was examined with this point in view.

An aliquot portion of the alcohol filtrate was evaporated to dryness in a vacuum evaporation apparatus at a temperature of 35 C. A drop of acetic acid was added to prevent the escape of any ammonia during the desiccation. The fatty residue after being mixed with sand was extracted with dry ether in a Soxhlet apparatus for forty-eight hours and the nitrogen content of the ether extract estimated. The results of complete analysis of the serum were as follows:

	Gm. per L.
Total alcohol-soluble nitrogen	0.53
Urea + ammonia nitrogen	0.28
Ammonia nitrogen.....	0.03
Ether-soluble nitrogen	0.19

The figure for ether-soluble nitrogen is probably too high since even with dry ether it is possible that some urea may go into solution. Also

9. Letsche: Beiträge zur Kenntniss der organischen Bestandteile des Serums. Ztschr. f. physiol. Chem., 1907, liii, 31.

there may be in blood, ether-soluble substances containing nitrogen that are not lipoids. In the case of a dog whose ureters had been ligated about the same percentage of ether-soluble nitrogen was found in the blood.

The method of precipitating the protein from blood by alcohol leads to no accurate conception of the relative proportions of the various nitrogenous fractions in the blood, since alcohol may be regarded as a selective solvent in which some substances would not go into solution (e. g., purins, in part), and hence not appear in the filtrate. It is of interest, nevertheless, to compare in this connection various samples of blood subjected to this same procedure. The accompanying table (Table 2) shows the results of analyses of uremic blood, compared with analyses of blood in acute renal suppression (sublimite poisoning) and with analyses of the blood of a dog whose renal arteries had been ligated about forty-eight hours before the blood was taken. The quantitative change in the filtrate

TABLE 2.—ALCOHOL-SOLUBLE NITROGEN (GRAMS PER LITER)

	Total N	Urea and Ammonia N	Per cent.	Ether- Soluble N	Per cent.
Human, normal (high)	0.62	0.41	66	0.22	35
Uremia	0.53	0.28	49	0.19	36
Uremia	2.14	1.78	83
Dog	1.86	1.41	75	0.58	31
Human HgCl ₂ poisoning	1.45	0.88	60

nitrogen resulting on the suppression of renal activity (mercury poisoning,¹⁰ ligation of renal artery¹¹) approaches that found in the severe grades of uremia. In the artificial conditions, however, there are none of the manifestations recognized clinically as uremia.

The question naturally arises at this juncture as to how much the quantitative deviations in the filtrate nitrogen represent purely a suppression of renal function and to what extent they may be interpreted as a morbid metabolic process. In order to gain any insight into this problem another method than that of removal of the blood proteins by alcohol must be employed. The requirements to be met by a suitable process are the removal of all the protein and fatty substances from the

10. Umber: *Charité Ann.*, 1903, xxvii, 160; v. Jaksch, *Leyden Festschr.*, 1902, i, 197.

11. Brown-Séquard: *Arch. de physiol.*, 1893, v, 777; Ascoli: *Berl. klin. Wchnschr.*, 1902, 561, 634; Soetbeer: *Ges. in Giessen*, 1908, xxiii, 6.

blood without affecting the solubility of other substances; in short, a separation of colloids. The method should not be harsh enough to cause the formation of cleavage products from the protein. On this score objection can be made to practically every method that has been employed in the chemical investigations of blood. The absorption methods of Rona¹² are perhaps least open to criticism, because no violent treatment of the blood is necessary, yet all the proteins are completely removed. Whether other substances than proteins are removed also can be determined only by control observations employing varied procedures.¹³

The kaolin adsorption method of Rona and Michaelis was devised to investigate the question of whether sugar exists in the blood in a colloidal state. Theoretically this method will remove from the blood only such substances as are held in colloidal suspension. It is always possible that other materials may be mechanically (or by adsorption) removed as well, but of this little is known. The chief objection in its application to the question under investigation is that hemoglobin is not readily adsorbed by kaolin, which necessitates the use of serum instead of whole blood. This, however, is not a serious deficiency as it is possible to derive purely comparable results. The method employed is to dilute the serum, one part of serum to fifteen or twenty parts of distilled water, five drops of strong acetic acid being added to the diluting water. The proportions in the dilution must be exact to admit of quantitative estimation. To the diluted serum kaolin is now added, 20 gm. of kaolin to each 100 c.c. of the fluid. The kaolin should be introduced in small portions, shaking the mixture repeatedly. After standing for an hour the material is filtered. If the procedure has been properly done a water-clear¹⁴ filtrate results which gives no biuret reaction. The filtrate from normal blood serum treated in this way yields a slight whitish precipitate with phosphotungstic acid reagent, but no effect is produced by Millon's reagent nor by potassium mercuric iodid. There is no precipitate with tannic acid or phosphomolybdic acid. In a number of instances the filtrate was concentrated in a vacuum pan at a temperature of 35 C. in order to render

12. Rona and Michaelis: *Biochem. Ztschr.* 1908, vii, 329, 1909, xvi, 60; Oppler and Rona, *ibid.*, 1908, xiii, 121.

13. If blood is a compound, as some investigators, notably of the French school, maintain, wherein all the different ingredients exist in a state of chemical union with each other, then any knowledge of the actual relationship must be out of the question at present.

14. Slight coloring of the serum with hemoglobin does not interfere with the recovery of a protein-free filtrate, but bloody serum can not be employed.

Dr. Walter Eddy endeavored to recover proteins from the kaolin mixture left on the filter and found that this could be effected only in part and that the process of recovery changed the proteins to metaproteins.

the above tests more conclusive. There was no change in the reactions in consequence of concentration.

The filtrate from uremic blood is not uniform in all of the reactions secured. There is, as with the normal, a slight precipitation on the addition of phosphotungstic acid. Both potassium mercuric iodid and Millon's reagent gave precipitates in a few instances, but these reactions were not common to all bloods examined. There was no precipitate caused by tannic acid.

The filtrate was examined after concentration for indol by means of indican, Obermayer's reagent, but it was not detected in any instance.

TABLE 3.—PARTITION OF NON-COLLOIDAL NITROGEN IN SERUM
SERIES C. CHRONIC NEPHRITIS

Case	Total Nitrogen, Grams	Urea-N+Ammonia N, Grams	Per Cent.	Purin N, Grams	Per Cent.	
19	0.68	0.471	70	0.048	7.3	Uremic coma; died
15	5.37	1.880	35	0.070	1.3	Uremic coma; anuria; died
7	2.16	0.970	45	Large white kidney, uremia; died
12	1.23	0.901	73	0.12	9.7	Chronic nephritis, incipient uremia; discharged improved
13	0.96	0.75	78	0.16	10	Second admission in uremic convulsions; discharged improved
20	0.78	0.308	39	0.066	9	Fatty degeneration of kidney, alcoholic wet-brain; death
22	0.81	0.38	47	0.143	17	Incipient uremia; discharged improved

SERIES. KIDNEYS, NORMAL

16	0.64	0.37	57	0.04	6.5	Gas poison
17	0.68	0.38	56	0.08	11	Gas poison
21	0.46	0.34	74	0.09	20	Gas poison

This is of special interest since Obermayer and Popper found indican peculiarly constant as an ingredient in uremic blood.¹⁵ The subject of indican in blood will be dealt with subsequently.

The quantitative estimations of the various nitrogen fractions in the filtrate were made by the usual methods; total nitrogen by the Kjeldahl method, urea by Benedict's, ammonia by Folin's and purins by the Kruger-Schmidt method. The results of these analyses are shown in

15. Since it seemed possible that indican might be removed by kaolin, urines were tested by mixing with kaolin and acetic acid. The filtrate gave reactions equally as strong as the untreated urine.

Table 3. The values found for the various nitrogen fractions are in general about the same as those of other investigators; in some cases, however, the absolute quantities are considerably higher, though the percentages are not exceptional.¹⁶

The notable feature in the results of these analyses as in Table 1 is the variability that is indicated in the amount of "filtrate" nitrogen in uremic blood. More than that, not only is the amount of total nitrogen bounded by no definite limits, but also the largest fraction of this total nitrogen, urea, bears no constant relation to the total. In fatal cases the urea nitrogen is 35 to 70 per cent. of the total nitrogen while in the less severe cases the extremes are 39 to 78 per cent. There is not in the results here recorded any substantial evidence in support of a possible abeyance of the urea-forming function which might lead to an accumulation of precursors of urea in the blood, since with some small mild cases, at least, the relative amount of urea is as low as with fatal cases. The absolute amount of undetermined nitrogen — which is the fraction of peculiar interest — in some instances (Case 15) suggests a very great concentration, but apparently this appears only when there is a high degree of renal suppression. It is surprising, perhaps, that this is the case, because with a failure to excrete urine the nitrogen substance chiefly affected would be urea, a relatively slight retention of which would increase the

16. v. Jakseh precipitated the proteins with phosphotungstic acid and found from 2 to 3 gm. per liter of "filtrate" nitrogen of which 95 per cent. was urea. These figures for total "filtrate" nitrogen are too low, since phosphotungstic acid precipitates many non-protein nitrogen compounds, v. Jakseh. See Note 10.

Ascoli used sodium chlorid and acetic acid to remove proteins. His values for total nitrogen are 0.94 gm. per liter in cases of atrophic kidney, 0.48 gm. in parenchymatous nephritis, and 0.99 gm. per liter in uremia. *Pfuger's Arch. f. path. Anat.*, 1901, lxxxvii, 103.

Straus employed heat and acetic acid to coagulate the proteins. He found an average of 0.8 gm. per liter in cases of interstitial and 0.39 gm. in parenchymatous nephritis. With uremia the "filtrate" nitrogen was increased to over 1 gm. per liter. He also noted considerable variations. *Die chronische Nierentzündung in ihre Einwirkung auf die Blutflüssigkeit und deren Behandlung*, Berlin, 1902, p. 68.

Umber precipitated by means of alcohol and fractionated the filtrate with phosphotungstic acid. The average amount of total nitrogen found was about 1.4 gm. per liter of which 90 per cent. was urea. This very high proportion is the result of the method. *Charité Ann.*, 1903, xxvii, 160.

Hohlweg used acetic acid, monopotassium phosphate and half saturation with sodium chlorid to free the blood from protein. In uremia he found considerable variation, between .8 and 3.0 gm. per liter, the latter amount representing the conditions shortly before death. In some cases of nephritis in which the patients died *without uremic symptoms equally high values* were obtained for the *total filtrate nitrogen*. *Deutsch. Arch. f. klin. Med.*, 1911, civ, 216.

Obermayer and Popper, using heat and acetic acid to coagulate the proteins, found the filtrate nitrogen in uremia between 0.7 and 4.4 gm. per liter, of which 21 to 90 per cent. is composed of urea. *Ztschr. f. klin. Med.*, 1911, lxxii, 333.

The estimations of Widal and his collaborators were made with the hypobromite method which is devoid of accuracy. Personal letter.

blood content considerably, both absolutely and relatively to the total nitrogen. That is to say, with pure retention, as noted in acute renal suppression, the "filtrate" nitrogen of the blood increases rapidly, and all of the factors composing "filtrate" nitrogen increase equally, so that ratios remain fairly constant. Urea nitrogen remains the chief component in the blood as it is in the urine so long as cellular conditions do not change and the percentage of total "filtrate" nitrogen recovered as urea is relatively high. The conditions that might be expected and are found in the blood with pure ablation of renal function are not uniformly fulfilled in the uremic state, although in individual cases they are suggested.

It would be premature to attempt to draw conclusions from data so lacking in accordance as those presented in this paper and it must be left to further investigation now in progress to disclose in uremic blood chemical substances which either quantitatively or qualitatively present a constant divergence from normal.

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THE EFFECT OF INTRASPINAL INJECTIONS OF RINGER'S SOLUTION IN DIFFERENT AMOUNTS UNDER VARYING PRESSURES *

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INTRODUCTION

This paper is presented as an experimental inquiry into the cause of the severe shock which sometimes follows the injection of serum into the subarachnoid space of the spinal cord. The sole object of this investigation has been to determine the mechanical effect on the spinal and medullary centers, of increasing the amount and pressure of fluid in the spinal subarachnoid space. For this purpose Ringer's solution has been used, as this contains the different inorganic salts of a *real* physiological salt solution, and is therefore preferable to the isotonic solution of sodium chlorid commonly called by that name.

No attempt has been made to use serum in any of these experiments, as it was desired to separate the mechanical effect from the obscure symptoms of serum-sickness sometimes produced by injecting a foreign blood-serum. For this reason Ringer's solution was selected, as it contains only the inorganic salts of blood-serum (sodium, calcium and potassium) in the proportion in which they exist in the normal blood.

In order that a post-mortem examination might determine where the fluid had been injected, and the parts to which it had extended during the experiment, an inert coloring matter was added to Ringer's solution. At first lamp black was tried, but proved unsatisfactory, as sedimentation quickly occurred. Liquor carmini was found to answer this purpose, as it is inert and non-diffusible. The carmin is held in solution by glycerin. A mixture of 20 per cent. liquor carmini and 80 per cent. Ringer's solution was found most satisfactory. In this proportion the amount of glycerin is only present in half the amount used in Toison's fluid, which is isotonic with blood corpuscles and commonly used for blood examinations.

IMPORTANCE OF SUBJECT AND OBJECT OF PRESENTING IT

Sudden death, with symptoms of collapse, extreme pallor, slow heart and cessation of respiration has been reported in some cases soon after the intraspinal injection of therapeutic agents used to produce spinal

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anesthesia. But it is not probable that spinal anesthesia will ever come into general use. However, since Flexner's discovery of an antimeningococcus serum, this method of medication has become an important one, as it offers the only hope of relief and has reduced the gross mortality from all cases of cerebrospinal meningitis to about one-fourth of what it formerly was, and in those cases in which the serum had a chance, to approximately one-eighth of the former mortality rate.

FORMER METHODS

Flexner advised the removal of an amount of cerebrospinal fluid equal to the volume of serum injected, thinking that thereby the intraspinal pressure would not be disturbed and any danger from that source could be avoided in this way. It has been found that this precaution is not

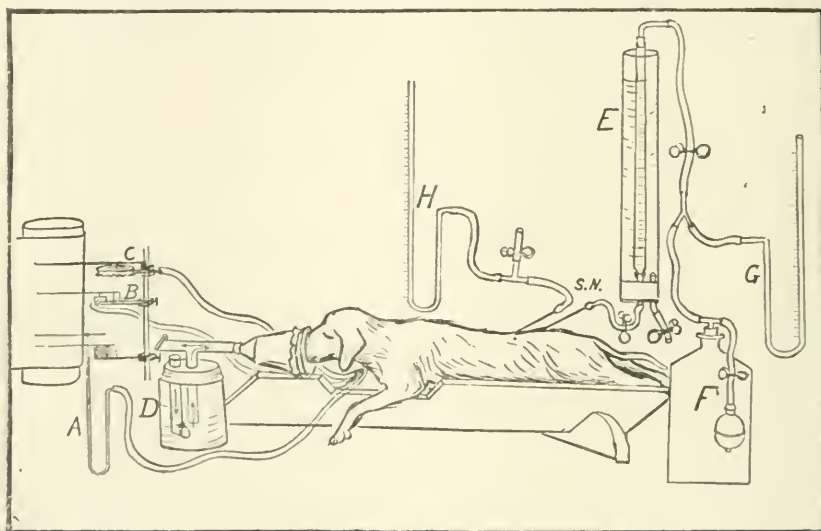


Fig. 1.—Apparatus used in author's experiments. For explanation see text.

sufficient to prevent sudden death in some cases, either during or soon after the injection.

During the recent epidemic in this state, Dr. Abraham Sophian¹ attempted to use the intraspinal pressure as a guide, but found it unreliable and unsatisfactory. Thus if the intraspinal pressure was found abnormally high when lumbar puncture was first made, he allowed the cerebrospinal fluid to escape until the pressure fell to normal (20 to 100 mm. of water, or from 2 to 8 mm. of mercury). Naturally one would expect that serum could then be injected with safety as long as the pres-

1. Sophian, A.: Jour. Am. Med. Assn., 1912, lili, 843.

sure did not exceed the original intraspinal pressure. Dr. Sophian states that the results by this method were misleading and unreliable.

The experiments presented in this paper show that in normal animals there is the greatest variation. In one the respiration will cease when the intraspinal pressure is increased to the equivalent of 10 to 15 mm. Hg; in others the intraspinal pressure may be increased above 50 or even 100 mm. Hg before alarming symptoms develop. The rapidity with which the pressure is increased seems to be important, but there is some other unknown factor of greater importance, probably the susceptibility of the individual. It may also be that the distribution of fluid injected varies in different animals, accounting for variations in the amount and pressure that may be used with safety in different cases.

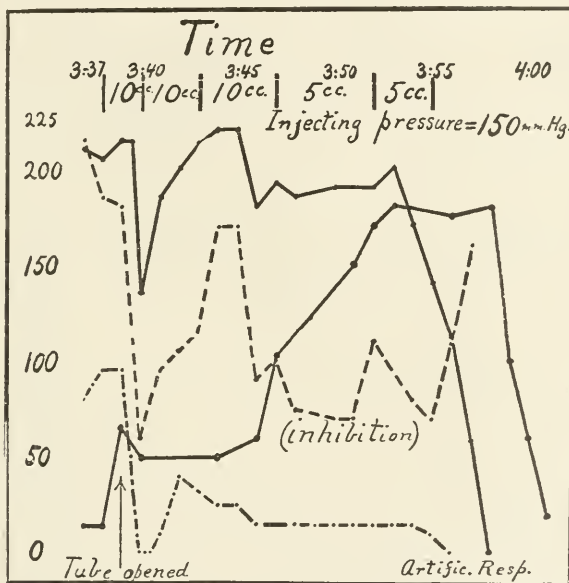


Fig. 2 (Experiment 5).—Dog's weight 17.73 kg. Upper continuous black line = blood-pressure; middle broken line = pulse-rate; lower broken line (—.—.—) = respiration; continuous line below = intraspinal pressure in mm. Hg.

If it is impossible to fix any limit of safety in increasing the intraspinal pressure in normal animals, it is manifestly hopeless to do so in meningitis in which an extensive inflammatory exudate may interfere with the passage of fluid through the spinal into the cerebral subarachnoid space.

Dr. Sophian has called attention to the great value of blood-pressure readings as a guide in withdrawing cerebrospinal fluid and in making injections into the spinal subarachnoid space. He states that a fall of blood-pressure equal to 20 mm. of mercury is a safe indication to stop

further injection; that a *sudden* fall should be a guide not only to the *quantity* but to the *rapidity* of injecting the serum. It is obvious that the injecting pressure and rapidity of flow can be controlled better by gravity injections than by using a piston syringe.

These observations are of the utmost importance, for they point out dangers which had not been previously understood and which are not as yet fully appreciated. With a fuller understanding of them we shall probably be able to avoid them. There are a number of reasons why it does not seem practicable for the general practitioner to adopt the method suggested by Dr. Sophian. Many physicians have not had experience in using the sphygmomanometer, and are not familiar with the method of making determinations of the blood-pressure; comparatively few have the special apparatus needed for making these operations; time is of such

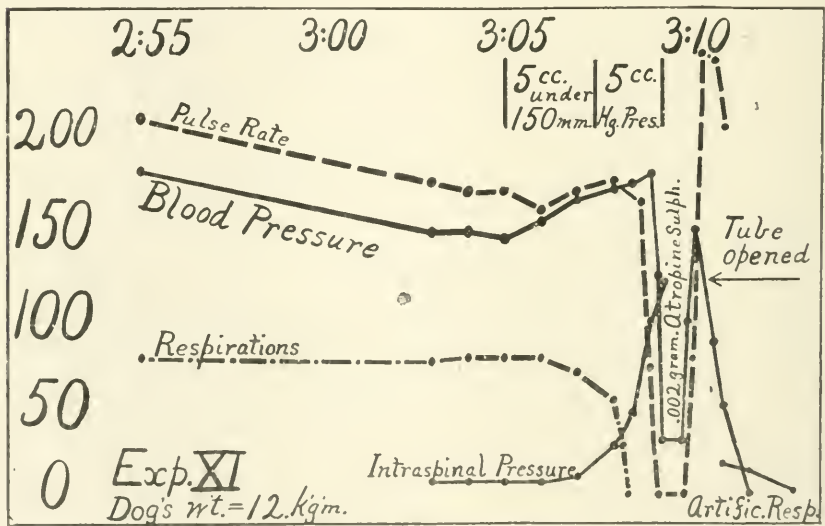


Fig. 3 (Exp. XI).—Curves showing sudden cessation of respiration, followed by complete cardiac inhibition for 30 seconds. Atropin relieved the cardiac inhibition but failed to restore respiration.

value in instituting proper treatment as soon as the diagnosis is established, that it is not always possible to secure the services of a physician who can take blood-pressure during intraspinal injections, unless it be in a hospital.

Again, the procedure suggested by Dr. Sophian of stopping the injection and giving smaller amounts of the serum at a time seems undesirable. The antimeningococcus serum operates locally by its bacteriolytic action. It seems especially desirable, therefore, to give as much as possible, within the limits of safety, in order that it may reach the base of the brain and exert its influence over the entire area involved. It would seem

more desirable to avoid the danger, if possible, than to limit the amount of the injection.

What are the mechanical effects of injecting any fluid into the spinal subarachnoid space? How are the alarming symptoms produced? How may they be counteracted, or what is more important, how may they be anticipated and prevented? These are the main questions which we shall endeavor to answer by the experiments presented in this paper.

PREVIOUS WORK ON THE SUBJECT

Cushing² investigated by experiments on dogs the effect of the cerebral compression. This was produced by physiological salt solution introduced under different pressures into the subdural space through trephine holes in the cranium, or into the subdural space in the spinal canal through trephine openings in the lamina of the upper vertebra.

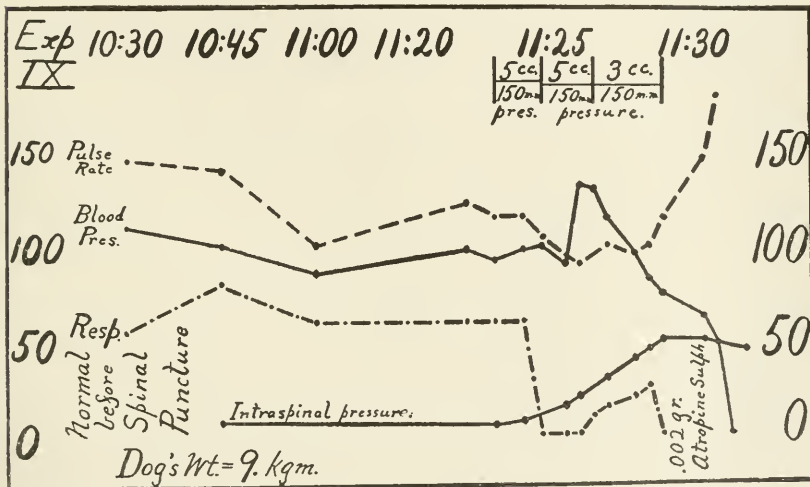


Fig. 4 (Exp. IX).—Curves of dog with abnormally low blood-pressure. A slight increase of intraspinal pressure caused the respiration to stop without cardiac inhibition. Atropin increased the pulse rate but failed to stimulate the respiratory center.

Cushing found that when the intracranial pressure is increased until it approximates the mean blood-pressure, there is pronounced cardiac inhibition, with very slow, shallow and often irregular respiration; that these effects are most pronounced when the intracranial pressure is increased rapidly and may cause complete cardiac inhibition, lasting from ten to twenty seconds; that this cardiac inhibition can be avoided by section of the vagi.

2. Cushing, H.: Bull. Johns Hopkins Hospital, 1901, xii, 290.

Cushing found that when the intracranial pressure approaches the mean blood-pressure a rise of blood-pressure follows, due to stimulation of the vasomotor center in the medulla. This regulatory action of the dominating vasomotor center is essential in maintaining the capillary circulation in the brain. In this way the blood-pressure may be raised to 200 mm. or even 250 mm. of mercury or more, and held there until the vasomotor center in the medulla becomes fatigued.

Rehn, quoted by W. C. Lusk,³ injected physiological salt solution into the spinal cord of animals without recognizable effects. It is probable that he only used small amounts, as he endeavored to find whether the effects of stovain, novocain and tropacocain were toxic or mechanical, when these drugs are used to produce spinal anesthesia.

METHOD OF EXPERIMENTATION

Dogs were used in all experiments. The blood-pressure was taken by canulas introduced into the carotid arteries. One was connected with a mercury

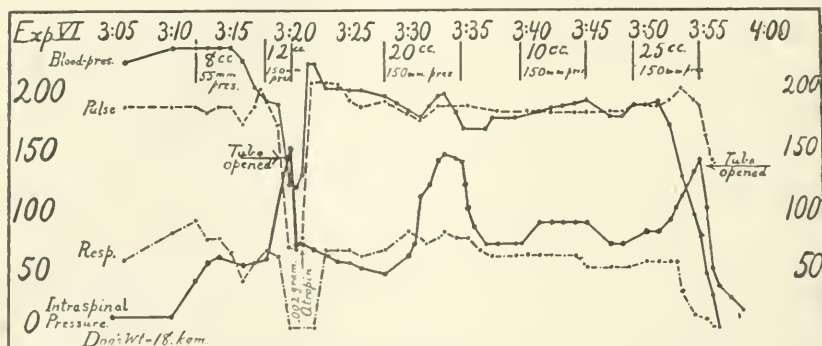


Fig. 5 (Exp. VI).—Typical experiment of Group II. An increase of intraspinal pressure caused pronounced cardiac inhibition coincident with cessation of respiration. The latter condition persisted for two minutes (one minute after the administration of atropin) but the cardiac inhibition completely disappeared within one-half minute after the injection of atropin. Subsequent intraspinal injection failed to produce cardiac inhibition.

manometer (Fig. 1, A) while the other was registered by a membrane manometer (B). The latter was used especially to detect any changes in the systolic pressure that might result from alterations in the force of the heart beats; also to show any change in the diastolic pressure in case the vasomotor tone might be disturbed, as in the production of ordinary shock.

A tube introduced into the trachea was connected with a tambour (C) for recording the respirations, and this was arranged to write on the revolving drum on the same vertical line as the writing styles of the two manometers mentioned above. The time was marked in seconds by an electromagnet.

Anesthesia.—The animals were kept under ether uniformly so that sudden changes in the circulation or respiration could not be attributed to the anesthetic used. For this purpose the inspired air passed through a Mason jar (Fig. 1, D)

3. Lusk, W. C.: Ann. Surg., 1911, liv, 449.

mixed with a perfectly uniform ether vapor arising from ether covering the bottom of the jar. Light respiratory valves of aluminum disks caused the exhaled air to escape without passing through the jar. The arrows in Fig. 1 show the direction of the currents of inspired and expired air. In this way there was no variation in the vapor density at any time, as the minimum amount of ether for maintaining light anesthesia was used.

This method of maintaining uniform anesthesia for long experiments has been used successfully in the laboratory for the past two years and eliminates from consideration any possibility of a complication from the anesthetic which could account for the profound disturbance of the respiration and circulation that results from intraspinal injections.

Mode of Injection.—The carmin-Ringer's solution was injected from a graduated buret so that small amounts could be measured accurately. The buret (Fig. 1, E) was connected with a needle used for spinal puncture by a short length of rubber tubing with a spring pinch-cock. A large glass tube, like that used for condensers, surrounded the buret. This was filled with luke-warm water constantly so that the fluid entered the spinal canal at the bodily temperature.

The injecting pressure, under which fluid was forced into the spinal canal, was exerted by compressed air. The bulb of an atomizer was attached to a T-tube in the stopper of a half-gallon bottle (Fig. 1, F); a piece of rubber tubing connected the bottle with the top of the buret; interposed between the two another T-tube connected with a mercury manometer (G) so that the pressure of the

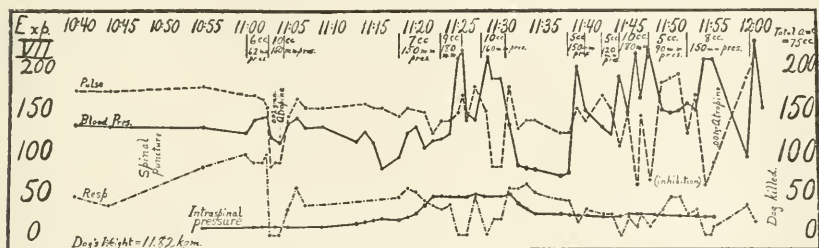


Fig. 6 (Exp. VII).—Another experiment of Group II illustrating the points mentioned under Fig. 5. The intraspinal injections made after the administration of atropin caused serious disturbance of respiration without dangerous cardiac inhibition. The blood-pressure rose from the late injections.

compressed air was measured accurately in mm. Hg, and could be kept uniform within variations of 5 mm.

Spinal Punctures.—These were made by needles used for giving serum in man. The lower one was introduced between the lumbar vertebræ at the level of the top of the pelvis; the second spinal needle was introduced one or two spaces above the first (Fig. 1, S. N.).

The injection was usually made through the lower needle, while the intraspinal pressure was usually taken by the upper one. The latter connected by means of rubber tubing with a mercury manometer (Fig. 1, H) with a T-tube interposed between the two. The side arm of the T enabled all air to be replaced by Ringer's solution; it also afforded a means of allowing fluid to escape quickly from the spinal canal, thereby lowering the intraspinal pressure.

Difficulty was experienced in getting needles of suitable size for spinal puncture in dogs. The smaller ones are easily occluded and offer great resistance to the flow of fluid through them; the larger ones are difficult to introduce between the vertebræ and often the beveled end punctures the spinal membranes without conveying all of the fluid into the subarachnoid space.

Spinal fluid escaped from the first needle introduced, but often it was impossible to get any from the second one, probably on account of the small amount and low pressure in the normal animal. Frequently the upper needle touched the spinal cord, but the blood-pressure was taken before and after the puncture. If any shock followed the introduction of the needles, time was allowed for this to pass off before starting the injections.

The intraspinal pressure was noted by one observer and called to another who recorded it immediately under the registration of the blood-pressure on the revolving drum. In some of the experiments the intraspinal pressure was recorded on the drum by a writing style on a mercury manometer, as Cushing made a tracing of the intracranial pressure.

Autopsies.—Immediately after each experiment an autopsy was made to determine if both needles had punctured the membranes, the location of the fluid injected, and the extent to which it had extended to the intracranial cavity.

The brain and cord were removed and fixed in 10 per cent. dilution of liquor formaldehydi in distilled water. The alkaline salts of tap water cause the solution and diffusion of some of the carmin injected.

RESULTS OF EXPERIMENTS

The first experiment was made with only one needle introduced into the spinal subarachnoid space. The intraspinal pressure was measured

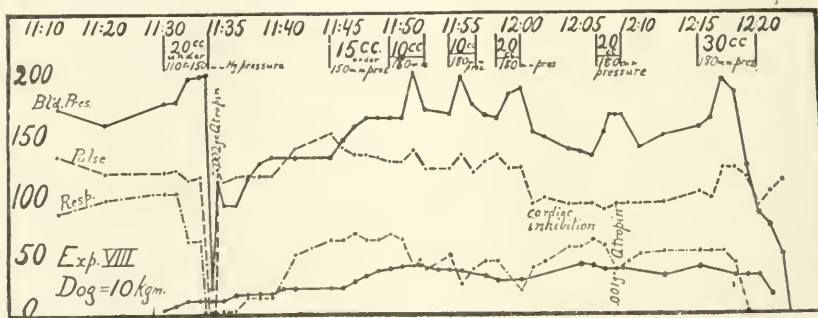


Fig. 7 (Exp. VIII).—Another experiment of Group II. A slight increase of intraspinal pressure to 10 mm. Hg caused sudden cessation of respiration followed by abrupt and complete cardiac inhibition. Atropin restored the normal heart beat within 10 seconds but spontaneous respirations only started after three minutes of artificial respiration.

Subsequent to the administration of atropin, the intraspinal injection of a larger amount of Ringer's solution, under a higher injecting pressure, failed to produce cardiac inhibition, but each injection reduced the respiratory rate greatly. The blood-pressure rose in these late injections as in Experiment 7 (Fig. 6).

before the injections, and again after they had been completed; but there was no increase over the normal (45 mm. Ringer's solution or 3 mm. of mercury).

Injections of 3 to 4 c.c. were made at a time, taking from two minutes to thirty seconds for each injection as the injecting pressure increased. Starting with an injecting pressure of 30 mm. of mercury, it was increased to 50, 80, 100, 120, 140, 160, 200, 230 and 250 mm. of mercury at succeeding injections.

A total of 29 c.c. was injected in a dog weighing 17.73 kilograms in the course of thirty minutes, with practically no effect until the injecting pressure had been increased above 100 mm. of mercury. With an injecting pressure between 120 mm. and 250 mm. of mercury, there was a moderate decrease of the respiratory rate, a slight increase of blood-pressure, with a decrease in the pulse-rate. The change was not more than one-tenth of the normal in any one, and the symptoms were not serious at any time. The animal was killed by chloroform. This experiment was remarkable for the slight disturbance produced by an enormous injecting pressure. The distribution of the pigment at the base of the brain and on the cortex showed that the fluid injected had reached the cerebral subarachnoid space, but evidently the pressure of fluid within that space had not been materially increased.

The intraspinal pressure was measured throughout the other experiments, but it was found that there is a wide variation in the extent to which it may be increased before alarming symptoms develop. In most instances a *rapid increase* in this pressure was the most important danger

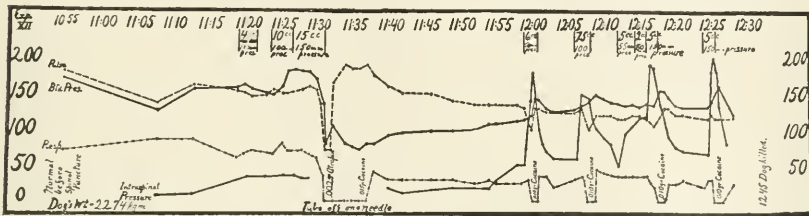


Fig. 8 (Exp. XII).—Experiment illustrating Group III. Atropin removed the cardiac inhibition immediately but failed to restore respiration. Although artificial respiration was kept up for five minutes, there was no attempt at spontaneous respiration. The injection of 0.010 gm. cocain started natural respiration at once.

Four injections after the administration of atropin caused cessation of respiration without cardiac inhibition; after waiting one minute for spontaneous respirations each time, the injection of cocain restored natural respiration promptly.

signal, but this was not constant, and no limit of safety can be fixed either as to the amount of fluid that may be injected, or the degree to which the intraspinal pressure may be increased.

In some experiments the most serious disturbance of the respiration and circulation occurred, with apparently very little or no increase of the intraspinal pressure. In these it is probable that the opening of the needle was occluded by membranes or by a clot, so that the actual intraspinal pressure was not registered by the manometer. Experiments 6 and 8 illustrate this point. Every effort was made to clear the needle when this condition seemed probable, but it is impossible to be certain that this is patulous when variations of pressure do not occur. In some experiments

no variations of intraspinal pressure could be obtained, and the injections were continued until characteristic symptoms developed.

In some experiments large amounts of fluid were injected with comparatively little increase of the intraspinal pressure. It is probable that this was due to some escape of the fluid to the extradural space, as it was often necessary to make a number of punctures in attempts to get the needles in the proper place. This condition obtained in the experiments of Group V.

In a few instances the intraspinal pressure rose rapidly, usually toward the end of the injection or immediately after it, and exceeded the injecting pressure recorded. This apparent discrepancy is explained by the fact that only the pressure of the compressed air was recorded as the injecting pressure. The column of fluid in the buret was not considered, as it was subject to variation. When the buret was filled it added a column of Ringer's solution 530 mm. in height, or a pressure of 40 mm. of mercury to that recorded as the injecting pressure. With the arrange-

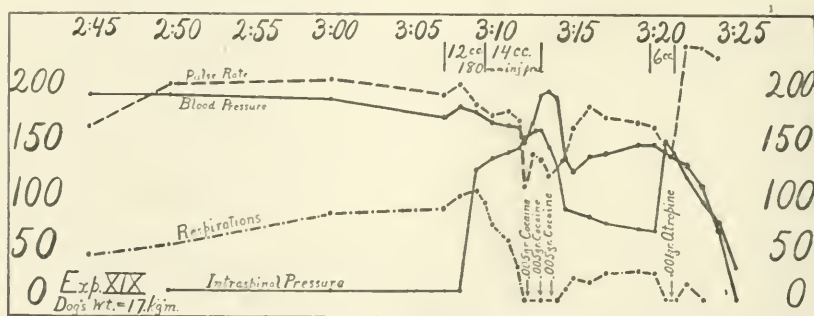


Fig. 9 (Exp. XIX).—This is one of eight experiments of Group IV, in which the cardiac inhibition was a less serious consequence of the intraspinal injection than the complete cessation of respiration.

The injection of cocaine restored natural respiration promptly, but this drug had practically no effect upon the cardiac inhibition. When subsequent intraspinal injections produced characteristic symptoms, atropin failed to restore respiration but caused cardiac inhibition to disappear promptly.

ment for keeping the fluid at body temperature, and for measuring the amount injected each time, it was impossible to overcome this difficulty.

Sudden variations of intraspinal pressure may occur during and immediately after intraspinal injections. Probably these are due to the distribution of the fluid injected in the subarachnoid or subdural space, variations of the intracranial pressure, or the blood in the plexus of the veins in the extradural space of the vertebral canal.

The experiments may be divided into five groups, and the diagrams on which the changes have been plotted show typical results better than a detailed description.

In the diagrams the time is given at the top. The time of each injection is marked by vertical lines; the amount injected and the injecting pressure are indicated between these vertical lines.

The numbers at the sides show the blood-pressure and intraspinal pressure in millimeters of mercury; also the pulse-rate and respiratory-rate per minute. The upper continuous line represents the blood-pressure; the upper broken line, the pulse-rate; the lower continuous line represents the intraspinal pressure; the lower broken line (— —) shows the number of respirations per minute.

GROUP I.—Experiments 5, 9 and 11 (Figs. 2, 3 and 4) were of brief duration. The injections caused death in a very short time from cessation of the respiration and pronounced cardiac inhibition. The respiration ceased from one to three minutes before the heart stopped, and in two of these experiments death occurred in spite of artificial respiration.

Lowering the intraspinal pressure relieved the cardiac inhibition temporarily in Experiment 5, but failed to do any good in Experiment 9.

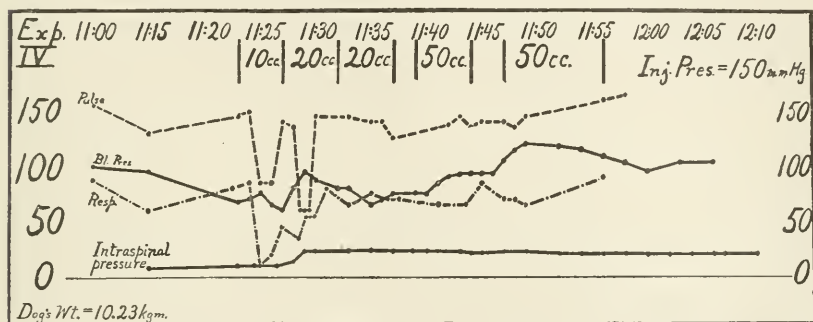


Fig. 10 (Exp. IV).—As a type of Group V. The first two injections produced some cardiac inhibition but subsequent injections of larger amounts had no effect. These exceptional results are explained by the escape of the fluid to the extradural space as described in the text.

The administration of atropin after alarming symptoms had developed (Exps. 9 and 11) caused the cardiac inhibition to disappear but failed to start the respirations, and the animals soon died.

In the experiments of this group comparatively small amounts of fluid were injected, viz., 10 c.c., 13 c.c. and 40 c.c. The injecting pressure (from compressed air) was 150 mm. of mercury, plus the column of fluid in the buret. The latter varied from the equivalent of 10 to 40 mm. of mercury, as previously explained.

Serious symptoms developed when the intraspinal pressure had been increased to 7 mm., 26 mm. and 66 mm. of mercury in the respective experiments. Fatal results occurred when the intraspinal pressure had been increased to 50 mm., 116 mm. and 180 mm. Hg.

The fall of blood-pressure was due entirely to the profound cardiac inhibition, probably from stimulation of the centers in the medulla. There was no loss of vasomotor tone as in surgical shock. The diastolic pressure recorded by the membrane manometer showed no change except that which occurs with cardiac inhibition. As soon as the latter disappeared from the administration of atropin, the systolic, diastolic and mean blood-pressure returned to normal. No attempt has been made to plot the systolic and diastolic pressure on the diagrams, as they show no change.

Two of the experiments of this group show unusually high blood-pressure (Exps. 5 and 11). In both instances the respiration ceased before the blood-pressure had been reduced to an abnormally low level by the pronounced cardiac inhibition.

This is of interest, for it shows that an abnormally high blood-pressure, such as occurs from increased intracranial pressure, is not sufficient to prevent the mechanical effects of intraspinal injections on the centers of the medulla. Robinson⁴ found that the blood-pressure was increased in a considerable proportion of the twenty-six cases of cerebrospinal meningitis patients studied by him, while it was decreased below the normal in others.

In Experiment 9 the blood-pressure was unusually low, as the animal was suffering from distemper. In this case the paralysis of the respiratory center was the most serious disturbance, while the cardiac inhibition was less conspicuous.

GROUP II.—In this group (Experiments 6, 7 and 8, Figs. 5, 6 and 7) pronounced cardiac inhibition, preceded by a cessation of respiration, occurred early in the experiment, after the injection of a comparatively small amount of fluid (6 to 20 c.c.). The administration of atropin promptly restored the circulation to normal and respiration was then reestablished.

A much larger amount of fluid (30 to 100 c.c.) was subsequently injected by repeated injections, some of them made under higher injecting pressure, without producing cardiac inhibition or serious fall of blood-pressure. The respiration ceased a number of times from the later injections, but it was not so easily affected in the absence of circulatory disturbances.

These experiments show that atropin prevents the effect of intraspinal injections on the heart but not on the respiration; also that the fall of pressure is not due to loss of vasomotor tone from depression of the vasomotor centers, but to cardiac inhibition.

Experiment 7 is of particular interest in this connection. The first injection had the usual effect. After atropin had been administered the subsequent injections caused a rise of blood-pressure, going above 200 mm. of mercury repeatedly, the elevation of pressure being proportionate to the

4. Robinson: THE ARCHIVES INT. MED., 1910, v, 482.

injecting pressure used. This must have been due to the stimulation of the vasomotor center in the medulla, as explained by Cushing. This experiment shows that intraspinal injections made by lumbar puncture may have the same effect that Cushing obtained by increasing the intracranial pressure, if cardiac inhibition is prevented. In spite of the rise of blood-pressure, the respiration ceased after each injection.

GROUP III.—Experiment 12 (Fig. 8) of this group differs from those of the preceding group, in that atropin did not restore the blood-pressure so promptly, although it immediately removed the cardiac inhibition. In this experiment there was decreased vasomotor tone, as shown by the low diastolic pressure. Natural respiration did not return after artificial respiration had been kept up for five minutes. The intravenous injection of cocain reestablished respiration at once.

Subsequent injections caused the respiration to cease without any material change of blood-pressure or pulse-rate. After waiting one-half to one minute, without artificial respiration or any sign of recovery, the injection of 0.010 gm. of cocain caused the normal respiratory rate to return. In this condition, as in ether narcosis, cocain is a valuable respiratory stimulant.

GROUP IV.—This group includes eight experiments, of which Experiment 19 (Fig. 9) shows typical results.

Characteristic symptoms (cessation of respiration and cardiac inhibition) followed the intraspinal injection, but the cardiac inhibition was less pronounced. Cocain was given alone, or it was given first and atropin was administered a considerable time later.

In each case cocain promptly restored the respiration, but failed to remove the cardiac inhibition. In some instances the cardiac inhibition was not lessened at all by the cocain; in others the cardiac inhibition gradually disappeared with the reestablishment of respiration to normal. The subsequent injection of atropin caused the immediate and complete disappearance of the cardiac inhibition.

This indicates that the cardiac inhibition is due to direct stimulation of the cardio-inhibitory center in the medulla, and does not result as one of the symptoms of asphyxia following the paralysis of respiration.

It is also obvious that both atropin and cocain are required to meet the disturbances of the circulation and respiration. Neither of them acting alone can meet the indications. It is also apparent that there is not sufficient time for using these drugs after alarming symptoms develop from intraspinal injections in man. In the experiments presented in this paper the injections were made directly into the jugular vein, but even then the result was uncertain.

The condition is analogous to the collapse which sometimes develops in chloroform narcosis from sudden stoppage of the heart due to cardiac

inhibition. It can easily be prevented by the preliminary administration of atropin, while all efforts at resuscitation often fail after a concentrated vapor of chloroform has produced the condition.

GROUP V.—Experiments 3, 4, 10, 13, 18, 22 and 25 (See Fig. 10 for Experiment 4) are remarkable for the large amount of fluid injected without the production of any symptoms or only mild and transitory disturbances. In these experiments the amount injected varied from 60 to 150 c.c., but the intraspinal pressure was low as a rule (See curves of Experiment 4).

The autopsy in each case showed a large amount of the carmin-Ringer's solution in the extradural space of the spinal canal. There was no pigment at the base of the brain or on the cortex and very little beneath the spinal arachnoid. Even the lining of the dura shows comparatively little pigmentation, so that most of the fluid must have been injected into the extradural space and doubtless escaped through the intervertebral foramina.

The failure to obtain any change in the circulation or respiration can easily be explained by the post-mortem finding, for an examination of the brains of these dogs shows that practically none of the fluid entered the cranial cavity and very little passed up the cord.

INCIDENTAL OBSERVATIONS

The question as to the distance to which fluid (c. g., serum) reaches when given by lumbar puncture can be definitely answered by the autopsy findings of the first four groups of experiments and by other preliminary experiments. Even small amounts under low pressure reach to the base and cortex of the brain.

Small amounts under moderate pressure probably do not reach into the lateral ventricles. At least carmin has only been found in those experiments in which a large amount of fluid had been injected under high pressure. Under these circumstances the lining of the ventricles is pigmented distinctly. It is doubtful if serum injected under the pressure which would be safe to use in man, ever reaches the lateral ventricles.

CONCLUSIONS

1. No definite limit can be fixed to which the intraspinal pressure may be increased with safety. In some animals serious symptoms developed when it was increased to 10 mm. of mercury, while in others this only occurred with a pressure of 50 or 60 mm. of mercury.
2. The normal intraspinal pressure in dogs varies from 3 to 10 mm. of mercury, or 40 to 135 mm. of water. A sudden increase of pressure, even though a small amount be given, is more dangerous than a larger amount given gradually by gravity.

3. The first mechanical effect of increasing the intraspinal pressure from injections made by lumbar puncture is the cessation of respiration; quickly following it, or coincidently with it, there is profound cardiac inhibition, which causes a tremendous and sudden fall of blood-pressure. The fall of pressure is often so abrupt that it frequently drops from normal to zero within a half minute.

4. Atropin removes the cardiac inhibition and restores blood-pressure by its paralyzant effect on the cardio-inhibitory nerve center.

5. Atropin fails to stimulate the respiratory center, while cocain is the most valuable respiratory stimulant for such an emergency.

6. These drugs should be given together in full doses before making a spinal puncture or intraspinal injection. The injection at the site of spinal puncture would also produce local anesthesia. The condition could thus be prevented more easily than it can be remedied after alarming symptoms suddenly develop. This is particularly true if chloroform is used as an anesthetic, as the inhalation of chloroform in concentrated vapor produces similar effects and thus makes the condition more serious.

7. The fall of pressure is not due to a vasomotor disturbance. There is, therefore, no indication for the administration of epinephrin. On the contrary, it is positively contra-indicated on account of its well-known action in producing cardiac inhibition.

8. Lowering the intraspinal pressure by allowing fluid to escape from the needle after the characteristic symptoms develop, fails to relieve the condition.

9. The advantage of using atropin and cocain before intraspinal injections consists not only of lessening the dangers of sudden death, but it enables a *larger amount* of fluid to be injected without producing dangerous symptoms from the mechanical effect. This is a great advantage in administering antimeningococcus serum, as its action is chiefly a direct, local one on the living bacteria and the benefits are in proportion to the amount administered.

TWO CASES OF ANAPHYLACTIC SERUM DISEASE OVER
SIX YEARS AFTER THE PRIMARY INJECTION
OF HORSE-SERUM (YERSIN'S ANTI-
PEST SERUM)*

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The widespread interest in hypersusceptibility and allergy and their relation to infectious disease leads me to report two cases of this nature following over six years after the primary injection of horse-serum.

I desire also to express the personal feeling that the use of diphtheria antitoxin for the immunization of *contacts* (the immunizing dose) should be avoided as often as practicable. I believe it is much wiser and shows more consideration for the patient for contacts to be examined from day to day and for cultures from the throat to be examined as well. In this way the disagreeable features of serum disease and the indiscriminate and widespread sensitization of many persons to horse-serum will be avoided.

Serum disease is a term used by von Pirquet and Schick¹ to denote the clinical manifestations following the injection of horse-serum. These symptoms may follow the primary, secondary, or other subsequent injection of serum. The first injection of horse-serum often causes symptoms peculiar to the serum itself, such as urticaria, fever, edema and joint pains. These are not due to the antitoxin, but to the horse-serum, and they only occasionally occur immediately after the injection. There is nearly always a latent or incubation period of eight to twelve days. Von Pirquet has noted that following the second injection of horse-serum, the reaction is altered as to time, quantity and quality; and these altered manifestations he has termed allergy (altered reaction).

With regard to the incidence of serum disease, Weaver² records that 31.1 per cent. of 692 patients with diphtheria to whom serum was administered, observed for ten days or more, exhibited the reaction.

The amount of serum injected to a great extent determines the appearance of the reaction. Thus, Weaver notes that when 1 to 9 c.c. of serum was administered, 10.9 per cent. of patients, observed for ten days or more, showed a reaction. When 100 to 109 c.c. were given, 44.4

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*Read at Meeting of Canal Zone Medical Association, May 8, 1912.

1. Von Pirquet and Schick: *Leipsic, Denticke*, 1905.

2. Weaver, G. H.: Serum Disease, *THE ARCHIVES INT. MED.*, 1909, iii, 485.

per cent. of patients showed a reaction; while in eight patients, given 170 to 280 c.c. of serum, all, or 100 per cent., showed a reaction.

Serum disease following a primary injection of horse-serum: This appears after an interval between the injection and the appearance of symptoms. At the end of the period of incubation, the symptoms suddenly appear. Locally, there is redness and itching of the skin. The general symptoms are fever, edema, skin eruptions, such as urticaria and erythema, swelling of lymph-nodes, leukopenia, joint pains, occasionally nausea and vomiting; there is some headache, backache and soreness and aching of the muscles, and in severe cases prostration and a tendency to fainting.

Serum disease following a secondary injection (toxic injection) given after a considerable interval: (Anaphylaxis). Ten days or more after a primary injection the exhibition of a second injection elicits symptoms of serum disease, either immediately or after a period of incubation shorter than that following a primary injection (allergy). The "immediate" reaction occurs within a day; while the "accelerated" reaction occurs usually within five to seven days after the secondary injection. The local symptoms are specific edema and urticaria at the site of inoculation. The general symptoms are fever, chilliness, exanthematous eruptions, urticaria, edema and joint pains, and in severe cases there is prostration and a tendency to fainting.

Von Pirquet³ states that after the first injection of horse-serum, serum disease appears seldom before the sixth day, oftenest on the eighth or ninth day, but frequently later. When individuals receive a secondary injection, the symptoms usually appear as an immediate reaction within twenty-four hours, and he noted that in children receiving a second injection, a number reacted on the sixth and seventh days. This von Pirquet and Schick called the "accelerated" reaction.

The secondary injection must be many times larger in amount than the minimum "sensitizing" injection in order to elicit visible symptoms; so that on this account it would seem to be impossible to determine by means of a cutaneous reaction whether an individual were sensitive to horse-serum.

Von Pirquet explains the phenomena of anaphylaxis or allergy as follows: In serum disease, for example, horse-serum is injected into man, and antibody is formed. We see at this time that symptoms of disease appear and the supposed connection is that the symptoms are due to toxic bodies formed by the digestion of the antigen (allergen) through antibody. On a second injection ("toxic dose") it is assumed (a) that the antibody is already present and when the horse-serum is injected the

3. Von Pirquet: THE ARCHIVES INT. MED., 1911, vii, 259 and 383.

toxic bodies are now formed and elicit an immediate reaction. It is assumed (b) if the second injection follows long after the primary injection the blood is free from antibody as well as horse-serum; but the body cells, however, having once made them, now make antibodies rapidly, so that in this case antibodies are formed more or less quickly. The toxic bodies are then formed and elicit the symptoms in an "accelerated" reaction.

In severe cases of serum disease there is more or less prostration and cardiovascular weakness. These symptoms are no doubt analogous to those elicited in experimental animals on the administration of secondary toxic doses of horse serum to sensitized subjects, and Auer⁴ has called attention to the interesting fact that symptoms and signs of anaphylaxis differ considerably in three species of animals which have so far been carefully studied. The characteristic drop in blood-pressure of dogs shown graphically so well by Pearce and Eisenbrey,⁵ is not found in the acute cases of anaphylaxis in the rabbit and guinea-pig. The large, pale, inflated lungs in the guinea-pig are not found in the dog or rabbit: and, again, the intravital rigor of the heart muscle in the rabbit is not seen in the dog or guinea-pig. In the rabbit Auer demonstrated that the heart itself is the vital cause of death in acute anaphylaxis in rabbits.

CASE REPORTS

Among the personnel at Ancon Hospital in May, 1905, S. T. D., who performed the autopsy, and H. W., an attendant, were exposed to a case of bubonic plague and each received 10 c.c. of Yersin's antipest serum. The same individuals, in October, 1911, were similarly exposed to a case of septicemic plague, and again received 10 c.c. of Yersin's antipest serum. At this time fifteen other individuals who had been exposed received injections of the serum. Among these was H. C. C., and of the seventeen persons injected, S. T. D., H. W. and H. C. C. developed serum disease, while none of the fourteen who had not been previously sensitized by horse-serum developed any symptoms of serum disease.

CASE 1.—S. T. D., physician, aged 39, had never had diphtheria, nor received injections of horse serum. He performed an autopsy on a case of bubonic plague June 23, 1905, and on this date received the equivalent of 10 c.c. of Yersin's antipest serum. This was a dried horse serum taken up with saline solution. No symptoms of serum disease followed the injection.

Oct. 17, 1911, nearly six years and four months later, he performed an autopsy on a case of septicemic plague and the following morning received 10 c.c. of Yersin's antipest serum (liquid horse serum). Following the injection there was some redness at the point of inoculation, but no other signs until October 23 (sixth day), when the skin area corresponding with the location of the injection

4. Auer: *Jour. Exper. Med.*, 1911, xiv, 493.

5. Pearce and Eisenbrey: *Jour. Inf. Dis.*, 1908, vii, 573.

itched intensely and an urticarial rash 6 to 7 cm. in diameter appeared there. The following morning (seventh day) the urticaria spread to the groins, inner aspects of thighs and the scalp. By noon almost all parts of the body above the knees were involved. While the pain and discomfort were severe, there were no other symptoms until 1.30 p. m., when he was awakened from a siesta by a feeling of intense depression as though fainting. The pulse could not be detected at the wrist. Yawning or sighing was frequent. A few minutes later the pulse was found to be 46, the features ashy-white, there was cold perspiration and an intense feeling of prostration. During the afternoon periods of intense stinging or tingling of the skin with tremendous edema of the scalp, lips, forehead and body were followed by attacks of prostration and feeble pulse. Each period lasted about fifteen minutes. There were also small circumscribed patches of pain in the epigastrium, esophagus (?) and right chest below the right nipple. On swallowing a glass of water on one occasion, it appeared that there was some swelling of the mucosa of the esophagus, for there appeared to be some resistance to the passage of fluid. During the afternoon attempts at rising and walking a few steps were quickly followed by fainting sensations and hallucinations of vision. Strychnin sulphate 1/30 gr. was administered hypodermatically in the left arm and the arm remained very tender and sore for two days. The intense itching kept up during the night but there was no distress or prostration. On October 25 there was some urticaria of the legs, particularly the soles of the feet. The patient could not sit up without discomfort. Large urticarial wheals appeared on the neck in the afternoon and there was some general neuralgia-like pain.

October 26: During the night there were large patches of urticaria on the knees and during the day backache and neuralgic pains all over the body. It appeared to the patient that the spells of depression or prostration were to some extent averted if the desire to scratch the areas of urticaria were controlled.

October 27 to 30: Patient felt weak, the muscles were sore and he had a haggard look. November 1: General feeling of well-being returned. November 2: A papular rash that itched or tingled slightly appeared on the breast and sides of chest from the fourth to the eighth ribs. This rash remained for three or four days.

CASE 2.—H. W., negro, native of Grenada, ward attendant. He received an injection of horse serum June 23, 1905. The secondary injection was received Oct. 18, 1911. Erythema at the point of inoculation was noted October 19. On the night of the twenty-sixth urticaria appeared and the patient awoke on the morning of the twenty-seventh at 2 a. m., feeling "stified." He took a drink of water and became covered with sweat. Could not go on duty this morning and remained off duty the twenty-eighth and twenty-ninth. Sticking pains in the chest were felt on the night of the twenty-sixth and twenty-seventh. Fainting sensations were experienced on getting out of bed or on taking an erect position after stooping over. On October 30 he returned to duty and for two or three days felt weak and sore in all his muscles.

H. C. C., who also developed symptoms of serum disease, was exposed to the case of plague of Oct. 17, 1911, and received on October 18, 10 c.c. of Yersin's antipest serum. October 20, local ("specific") urticaria appeared at the site of inoculation. October 26 there was swelling of the arms, face and hands with more urticaria at the point of inoculation, and slight vertigo on rising.

H. C. C. had received horse serum previously; September, 1906, 5 c.c. + — diphtheria antitoxin. September, 1906, 5 c.c. + — diphtheria antitoxin. October, 1906, 15 to 20 c.c. + — diphtheria antitoxin.

Shortly after the October (1906) injection local urticaria of the thigh appeared, and ten days after the injection of serum there was tremendous universal edema, with edema of the throat and larynx, causing some anxiety among his confreres. Between October, 1906, and April, 1907, he received diphtheria antitoxin several times, and on one occasion had a measles-like rash.

In this small series of cases of anaphylactic serum disease, only three of the seventeen individuals receiving serum experienced any symptoms of serum disease, and each one of these three persons had previously been sensitized by injections of horse-serum. S. T. D. and H. W. six years and four months, and H. C. C. five years previously. On this last occasion, H. C. C. had a late "immediate" (?) and an "accelerated" reaction. S. T. D. had an "accelerated" reaction and H. W. had a late "accelerated" reaction.

Considering the fact that the only individuals who suffered from serum disease were those who had been sensitized by previous injections of horse-serum, and on account of the very disagreeable symptoms and consequent loss of time from business, together with the doubtful value of Yersin's serum in preventing or aborting an attack of plague, its indiscriminate use for the immunization of contacts is considered inadvisable.

THE PATHOGENESIS OF PURPURA HEMORRHAGICA WITH ESPECIAL REFERENCE TO THE PART PLAYED BY BLOOD-PLATELETS *

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The hemorrhagic diathesis of chloroform and phosphorus poisoning is without doubt due to a deficiency of fibrinogen in the blood and that of a type of melena neonatorum to a retarded rate or complete failure of blood coagulation. The hemorrhages of jaundice and hemophilia can perhaps be accounted for by abnormal blood coagulation, although proof of this is not so clear as in the former diseases. The disease with which I shall deal in this paper, namely purpura hemorrhagica, has apparently an entirely different pathogenesis and, it is believed, is due wholly or partly to an almost complete absence of platelets from the blood.

HISTORICAL REVIEW

That the number of platelets in the blood is reduced in purpura hemorrhagica was first observed in 1887 by Denys, a histologist, and later by Hayem, the discoverer of blood-platelets. Denys¹ reported three cases in which platelets could hardly be found in fresh blood films. Hayem,² in three cases of idiopathic purpura hemorrhagica, made counts of 89,900, 62,000 and 41,000, and in two cases of symptomatic purpura hemorrhagica reported with Bensaude,³ noted a scarcity of platelets in blood films. Bensaude and Rivet,⁴ working in Hayem's clinic, studied stained and fresh blood films in five cases of chronic purpura hemor-

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*Results reported in brief before the Johns Hopkins Medical Society, Feb. 19, 1912.

1. Denys, J.: (a) *Études sur la coagulation du sang dans un cas de purpura avec diminution considérable des plaquettes*. La Cellule. 1887, iii; (b) *Un nouveau cas de purpura avec diminution considérable des plaquettes*. La Cellule. 1889, v; 189; (c) *Blutbefund und Culturversuche in einem Fall von Purpura hämorrhagica*. Centralbl. f. Path. u. path. Anat., 1893, iv, 174.

2. Hayem, G.: *Du purpura*, Presse méd., 1895, 233.

3. Hayem, G., and Bensaude, R.: (a) *Leucémie aiguë à forme de purpura hémorrhagique. Non-retractilité de caillots sanguins*. Bull. et mém. Soc. méd. d. hôp. de Paris, Feb. 13, 1903; (b) *Sur la non-rétractilité du caillot et l'absence de formation de sérum dans la variole hémorrhagique primitive. Mécanisme des hémorragies*. Soc. de biol., Jan. 19, 1901.

4. Bensaude, R., and Rivet, L.: *Les formes chroniques du purpura hémorrhagique*, Arch. gén. de méd., January, 1905.

rhagica and stated that the platelets were reduced in number. Coe,⁵ in five cases of hemorrhagic diathesis, found a reduced number of platelets. Three of his counts were 29,000, 22,000 and 25,000. The other determinations were made by examining stained blood-smears. Helber⁶ observed a case of purpura hemorrhagica in which the platelet count was 40,000. Ehrlich⁷ and Müller⁸ each report having seen a case similar to those reported by Denys. Pratt,⁹ in a case of purpura hemorrhagica complicating nephritis, made a count of 9,000. Selling,¹⁰ in studying purpura hemorrhagica complicating benzol poisoning, found in one instance a platelet count of 3,000. In another he noted an almost complete absence of platelets from blood-smears. Matthews and Carpenter,¹¹ in a convalescent case of purpura hemorrhagica found the count to be 18,700. Larabee,¹² in two cases of hemorrhagic diathesis in aplastic anemia, found a scarcity of platelets in blood-smears. In a previous paper¹³ I reported three cases of severe hemorrhagic diathesis in which platelet counts made during periods in which pathologic hemorrhage was present were all below 32,000. In each of these cases a large number of platelets were introduced into the circulation by direct transfusion of blood. Immediate and complete relief followed this procedure and persisted until the platelets introduced had disappeared. When the counts reached their previous low levels hemorrhage returned. The period of relief was attributed directly to the increased number of the blood-platelets.

A few low platelet counts have been reported in patients in whom hemorrhagic diathesis was not evident. Osler,¹⁴ Riess¹⁵ and others have found them reduced in pernicious anemia; Determann,¹⁶ in a case of nephritis (88,000) and in a case of pneumonia (40,000). Low counts

5. Coe, J. N.: The Treatment of Purpuric Conditions and Hemophilia. *Jour. Am. Med. Assn.*, 1906, xlvii, 1090.

6. Helber, E.: Ueber die Zählung der blutplättchen im Blute des Menschen und ihr Verhalten bei pathologischen Zuständen. *Deutsch. Arch. f. klin. Med.*, lxxvi, 317.

7. Ehrlich: Die Anämie, 1898, 134.

8. Müller, H. F.: Ueber einen bisher nicht beobachteten formbestandteil des Blutes. *Centralbl. f. allg. Path. u. path. Anat.*, 1896, vii, No. 13, p. 531.

9. Pratt, J. H.: Osler's Modern Medicine, 1907, iv, p. 681.

10. Selling, L.: A Preliminary Report of Some Cases of Purpura Hemorrhagica Due to Benzol Poisoning. *Bull. Johns Hopkins Hosp.*, 1910, xxi, 33.

11. Matthews, A. C., and Carpenter, H. P.: Purpura Hemorrhagica with Report of an Atypical Case. *Am. Jour. Med. Sc.*, July, 1911.

12. Larabee, R. C.: Aplastic Anemia, with Report of a Case. *Am. Jour. Med. Sc.*, July, 1911.

13. Duke, W. W.: The Relation of Blood Platelets to Hemorrhagic Disease. *Jour. Am. Med. Assn.*, 1910, iv, 1185.

14. Osler, William: Cited by Riess, Note 15.

15. Riess, L.: Bemerkungen über die Zerfallskörperchen des Blutes und ihr Verhältniss zur Anämie. *Berl. klin. Wehnschr.*, 1879, xvi, 696.

16. Determann: Klinische Untersuchungen über Blutplättchen. *Arch. f. klin. Med.*, 1898, ix, 365.

have also been found in lymphocytic leukemia, aplastic anemia and typhoid fever. Hayem, Riess, Wright and Kinnicutt and others found the platelet count reduced during the febrile period of several acute diseases. Hayem states that his lowest counts were in cases of purpura hemorrhagica.

GENERAL CONSIDERATIONS

It was seen early in this work that patients with purpura hemorrhagica of the type associated with an enormously reduced platelet count had a tendency to bleed from every trivial abrasion of the skin or mucous membranes. Frequently it was noticed that a patient bled for hours from a prick in the lobe of the ear or from a mere scratch on the skin. In some cases even the chewing of coarse food caused the gums to bleed. A slight blow, or even the rubbing or scratching of the skin, resulted in the formation of ecchymoses. Patients entering the hospital with severe symptoms were improved by the avoidance of all possible injury. In some cases extensive purpura cleared and hemorrhage from mucous membranes stopped almost completely following simple rest in bed. That there was little or no change in the general condition to account for this improvement was evidenced by the fact that a prick in the lobe of the ear would bleed for several hours.. It seemed obvious that the observation of symptoms alone would lead to false conclusions as to the severity of hemorrhagic diathesis. It was several times noted, for example, that ambulatory patients with the disease in mild form displayed more purpura and more profuse hemorrhage from mucous membranes than the severer hospital cases. For this reason conclusions in this study have been based but partly on symptoms shown by the patient. More reliable data was gained by observing their tendency to bleed from fresh cuts. This was studied by a means outlined briefly by me in a previous paper¹³ and called "the bleeding time."

THE BLEEDING TIME

The bleeding time is determined as follows: Make a small cut in the lobe of the ear. At half minute intervals blot up on absorbent paper all the blood which has flowed out. This gives a series of blots. Each blot represents the volume of blood flowing out in its respective half minute. From the rate of decrease in the size of the blots one can see at a glance the rate of decrease in the intensity of the hemorrhage. The duration of such a hemorrhage is called the bleeding time.

On first thought one might believe that the bleeding time depends largely on the size of the cut. This, however, within certain limits, is not the case. Figure 1 (a, b, c) are three normal bleeding times obtained from cuts of different sizes. The blots obtained from the largest cut (c) decrease in size even more rapidly than those obtained from the smallest cut (a). If hemorrhage from these cuts can be considered capillary hemorrhage, it is evident that a large number of capillaries stop bleeding

as rapidly as a small number. In marked contrast to the above is the prolonged bleeding time shown in Figure 2. This bleeding time was obtained from the smallest needle prick. The twentieth blot is practically as large as the first. Such a hemorrhage has been known to continue for more than two hours.

When the blots decrease rapidly in size the bleeding time is considered normal (one to three minutes). When they decrease more slowly in size and stop in from five to ten minutes it is considered slightly prolonged. Such is occasionally seen in severe anemia. When the twentieth blot is half the size of the first the bleeding time is moderately prolonged, and when as large as the first, is enormously prolonged.

The bleeding time is practically never more than slightly prolonged in normal individuals — at least such has been my observation during a period of three years.

It is prolonged in some types of hemorrhagic disease and not in others. It is enormously prolonged in chloroform poisoning when the decrease in the fibrinogen content of the blood is great. It is also enormously prolonged in purpura hemorrhagica of the type associated with a reduced platelet count. In these two diseases the bleeding time gives reliable information as to the severity of the hemorrhagic diathesis. It usually ranges from twenty minutes to several hours when the symptoms are severe, and drops to normal the moment the condition is relieved.

The bleeding time in my experience is normal in all forms of purpura simplex and jaundice. Observations have been made on patients with the following varieties of purpura simplex: idiopathic purpura simplex; purpura secondary to nephritis and septicemia; purpura rheumatica; Henoch's complex; scurvy; senile purpura; cachectic purpura, and purpura showing a segmental distribution. Observations have been made on patients with jaundice associated with a normal coagulation time and no hemorrhage; with a slightly delayed coagulation time and severe purpura hemorrhagica; and with an enormously prolonged coagulation time (thirty minutes and more) with and without evidence of pathologic hemorrhage. In all the above patients the bleeding time was less than three minutes. The platelet count was normal or slightly increased.

The bleeding time is, therefore, limited in its usefulness and can be employed to advantage in certain types of disease only.

OTHER METHODS

The coagulation time was determined by a simple method described by me^{15, 17} in previous papers.

The fibrinogen content of the blood in humans was estimated roughly by observing the firmness of blood-clots. It was estimated quantitatively

17. Duke, W. W.: A Simple Instrument for Determining the Coagulation Time of the Blood. *THE ARCHIVES INT. MED.*, February, 1912, ix, 258.

in dogs by a heat precipitation method as described by Whipple and Hurwitz.¹⁸

Retractility of the clot was studied as by Hayem.^{2, 19} Two c.c. of blood were collected in a small test-tube and allowed to stand at room temperature for forty-eight hours. Normally the clot separates itself in a short time from the sides of the vessel containing it and extrudes serum.

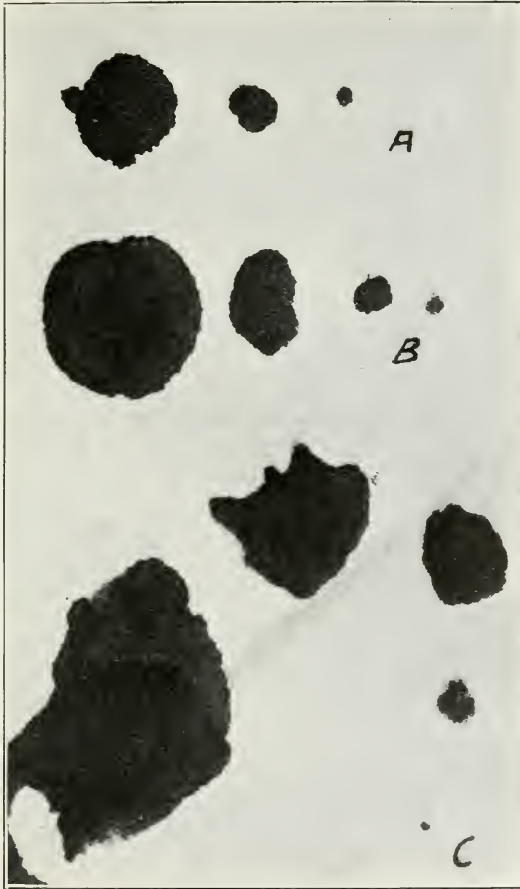


Fig. 1.—Normal bleeding times: A, from small cut; B, from larger cut; C, from very large cut.

Under certain pathologic conditions retraction fails to take place and little or no clear serum can be seen.

18. Whipple, G. H., and Hurwitz: *Jour. Exper. Med.*, 1911, xiii, 136.

19. Hayem, G.: *Du Caillot non rétractile: Suppression de la formation du sérum sanguine dans quelque états pathologique.* *Compt. rend. Acad. d. sc.*, 1896, cxxiii, 894. Cited by Bensaude.

The platelet counts were made by Wright and Kinnicutt's method,²⁰ with precautions mentioned by me²¹ in a previous paper. This method presents several advantages over other methods. It is simple and can be carried out with the ordinary blood pipets and counting chamber. The platelets are stained by the diluting fluid and thus rendered easily recognizable. The red cells are laked. The limit of error in counting platelets is somewhat greater than in red or white cell counts. The pathologic variation in the platelet count is so great, however, that an error of 10 to 20 per cent. may be considered negligible.

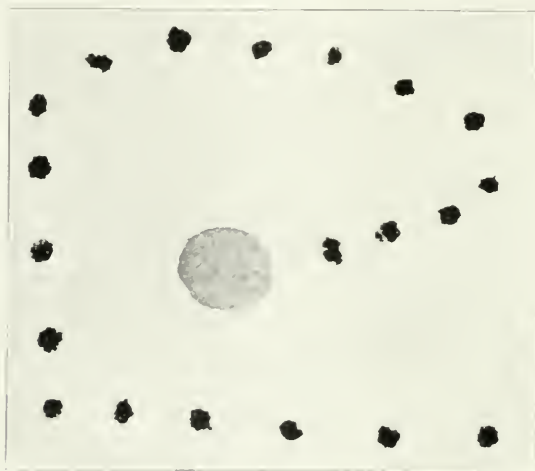


Figure 2.

The following counts were made in four normal individuals:

TABLE 1.—NORMAL PLATELET COUNTS IN FOUR INDIVIDUALS

Date	I	II	III	IV
May 9	275,000	295,000	290,000	315,000
May 10
May 11
May 12	220,000	300,000	280,000	240,000
May 13
May 14	280,000
May 15	270,000	190,000
May 16	225,000	300,000	300,000
May 17	220,000
May 18	240,000	190,000
May 19	230,000	350,000
May 20	225,000	275,000
May 21	260,000
May 22	196,000	400,000
May 23	220,000
May 24	210,000	250,000
Highest count	275,000	300,000	400,000	315,000
Lowest count	196,000	240,000	250,000	190,000
Average count	224,000	264,000	306,000	231,000

20. Wright, J. H., and Kinnicutt, Roger: A New Method of Counting the Blood Platelets for Clinical Purposes. Jour. Am. Med. Assn., 1911, lvi, 1457.

21. Duke, W. W.: The rate of regeneration of blood platelets. Jour. of Exper. Med., 1911, xiv, 265.

REPORT OF CASES

In the following study an effort was made to find some relationship between hemorrhagic diathesis and the condition of the blood. Hemorrhagic symptoms, the bleeding time, the platelet count and blood coagulation were studied in all cases which displayed a pathologic tendency to bleed, seen during the past three years. In many of the cases no abnormality of the blood could be discovered. In a certain group, however, the platelet count was constantly and enormously reduced. This group differed in many respects from the group having normal counts: in fact,

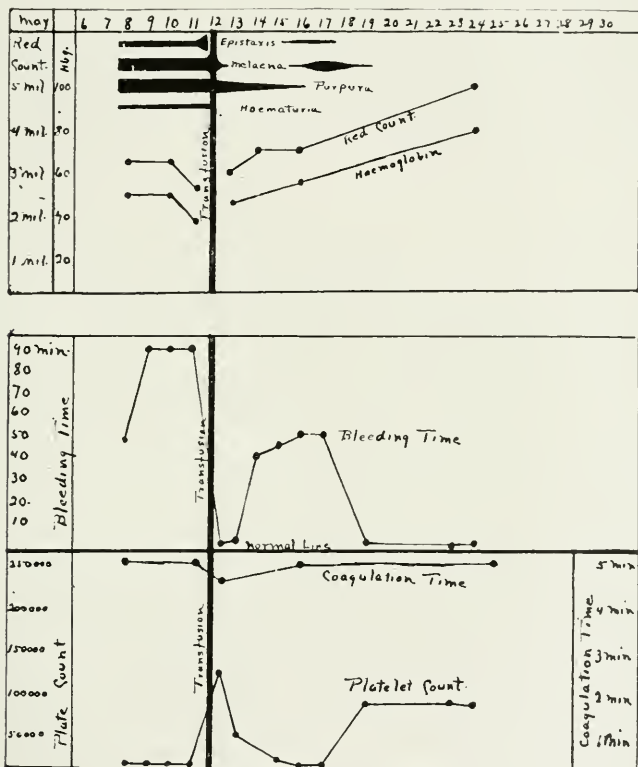


Fig. 3.—Chart of Case 1.

it became possible from the history and examination of a patient with well marked hemorrhagic diathesis, to correctly predict whether the platelet count was about normal or was greatly reduced. Subsequent discussion will be confined to the platelet-free group of cases, a detailed report of thirteen of which is as follows:

CASE 1.—*Idiopathic purpura hemorrhagica with result of transfusion.* (Case observed in the Massachusetts General Hospital, Boston, for more complete report of which see reference 13.)

History.—S. M., man aged 20, tailor. Family and past history unimportant. For four days before admission to the hospital the patient suffered from malaise, epistaxis, bleeding from the gums, hematuria, melena and had noticed a purpuric rash. Results of physical examination unimportant except for pallor and a generalized fine petechial rash. Petechias were seen even on the conjunctiva, mucous membrane of the mouth, the soles of the feet.

Laboratory Examination.—Stools and urine not remarkable except that they contained a considerable quantity of blood.

Platelet count 6,000. Bleeding time 60 minutes. Coagulation time normal (5 minutes). Clot firm and non-retractile.

Leukocytes varied from 2,400 to 7,000. Polymorphonuclears 80 per cent. to 86 per cent. Remainder mainly lymphocytes. One blast seen. Erythrocytes on admission 3,264,000. Hgb. 50 per cent. Sahli. Appearance of red cells normal.

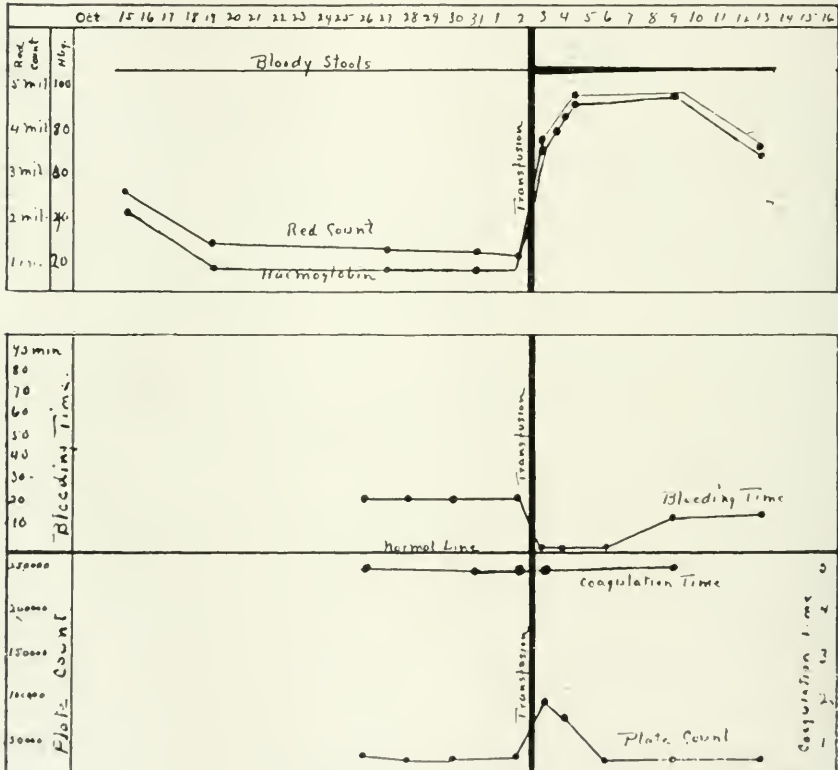


Fig. 1.—Chart of Case 2.

Course of the Disease.—The symptoms and laboratory findings were practically unchanged during the first four days in the hospital. On the fifth day a direct transfusion of blood was successfully carried out by Dr. F. T. Murphy. Following this there was complete cessation of all hemorrhage and the purpuric flecks began to fade. The platelet count was increased by transfusion to 123,000. The bleeding time was reduced to normal. The coagulation time was unchanged. The clot was retractile.

The number of platelets in the blood decreased rapidly after transfusion, and on about the fourth day reached its previous low level. At this time epistaxis

began again and fresh blood appeared in the stools. The bleeding time was again enormously prolonged. The coagulation time was unchanged. The clot was again non-retractile.

This condition continued practically unchanged for six days. On the seventh day there was complete cessation of epistaxis and there was no more blood in the stools. Platelets were present in the blood in abundance. The bleeding time was normal. The coagulation time was unchanged. The clot was normally retractile.

No purpura appeared during the second hemorrhagic period. The patient, during the following year, had no return of hemorrhage.

CASE 2.—Chronic intestinal bleeding in a boy with chronic ulcerative colitis. Results of transfusion. (Case observed in the Massachusetts General Hospital, Boston, for more complete report of which see Reference 13.)

History.—A. C., boy, aged 8. Family history negative. Since the age of 2 the patient had suffered almost continually from diarrhea. For four periods of a month or less, the stools contained considerable blood. The stools had contained blood for more than a month before admission to the hospital and the patient was pale and weak. Physical examination was unimportant except for pallor. There were no ecchymoses and no bleeding from normal mucous membranes while under observation. The stools contained mucus and pus and considerable fresh blood.

Laboratory Examination.—Platelet count 32,000. Bleeding time moderately prolonged (20 minutes). Coagulation time 5 minutes; clot firm; retractility diminished.

Leukocytes 2,200 to 4,700. Polymorphonuclears 40 per cent. to 60 per cent. Remainder mainly lymphocytes. Erythrocytes 1,600,000. Hgb. 20 per cent. Appearance of reds normal. No blasts.

Course of the Disease.—Symptoms and laboratory findings continued unchanged for seven days. On the eighth day direct transfusion of blood was successfully carried out by Dr. Hugh Cabot. The platelet count, made just after transfusion, was 89,000. The bleeding time was normal. The coagulation was unchanged. The clot was normally retractile.

The platelet count decreased steadily after transfusion, and on the fourth day had reached its previous low level. The bleeding time was then again prolonged. Conditions continued about the same until the boy's death, several weeks later.

Comment: This case is of interest in showing a striking difference between the effect of transfusion on normal and pathologic hemorrhage. The amount of blood in the stools was increased by transfusion in spite of the fact that the general tendency to bleed, as shown by the shortening of the bleeding time, was less marked. The intestinal hemorrhage, as shown by autopsy, proceeded from extensive intestinal ulcerations and cannot, therefore, be considered entirely pathologic hemorrhage. The increased hemorrhage following transfusion was thought to be due to the increased filling of the blood-vessels.

CASE 3.—Severe purpura hemorrhagica in a man with phthisis. (Case observed in Professor Romberg's clinic, Tübingen.)

History.—W. F., man aged 26, a weaver. Family history good. Past history negative except for attacks of migratory polyarthritis at the ages of 17 and 19. At the age of 16 and 21 he had nose-bleed for a short time. For five months he had had symptoms of phthisis and was in the hospital for this.

Physical Examination.—The patient was the picture of rather advanced phthisis. There were signs of considerable consolidation and possible cavity formation at both lung apices. The fingers were moderately clubbed. The daily temperature varied from 36 to 38 C.

Present Illness.—On May 13 the platelet count made as routine was 210,000, and the bleeding time was normal. Four days later, without other change in symptoms, the patient had profuse epistaxis and bleeding from the gums. He had continued bleeding from a hang nail on the thumb, also hematuria, melena, and hemorrhages from acne lesions on the face. A fine petechial rash was present on the abdomen and legs. The slightest rubbing brought out new flecks.

Laboratory Examination.—The bleeding time was enormously prolonged (over two hours). The platelet count was 4,000. Coagulation time normal (5 min.), clot firm and non-retractile. Leukocytes 19,000. Polymorphonuclears 74 per cent. Lymphocytes 16 per cent. Eosinophils 10 per cent. Basophils 0 per cent. No blasts. Reds normal in appearance, size and shape. Hemoglobin 80 per cent., Sahli. Urine and stools normal except for the presence of fresh blood. Sputum contained many tubercle bacilli.

Course of the Disease.—On the following day no platelets could be found, either in stained smears or in counting chambers. Their presence, in small numbers, was demonstrated, however, by examining the undiluted plasma by Bürker's

TABLE 2.—RESULTS OF DAILY EXAMINATION OF BLOOD IN CASE 3

Date	Platelet Count	Bleeding Time	Hemorrhages
May 14	210,000	Normal	None
" 17	Severe
" 18	4,000	Extreme delay	Severe
" 19	Below 1,000	Extreme delay	Severe
" 20	10,000	Extreme delay	Severe
" 21	Below 1,000	Extreme delay	Severe
" 22	110,000	Normal	None
" 23	210,000	Normal	None
" 24	295,000	Normal	None
" 26	385,000	Normal	None
" 27	520,000	Normal	None
" 28	550,000	Normal	None
" 30	720,000	Normal	None
June 1	720,000	Normal	None
" 7	640,000	Normal	None
" 12	400,000	Normal	None
" 17	500,000	Normal	None

method. Fibrin was present in abundance in this preparation and consisted of thick fibrils. There was no change in either symptoms or laboratory findings until May 22, when all hemorrhages ceased as suddenly as they had set in. The platelet count had suddenly increased to 110,000. The bleeding time had dropped to normal. The coagulation time was not noticeably changed. The clot was normally retractile. During the two months following there was no further bleeding.

The results of the daily examinations are contained in Table 2.

CASE 4.—*Idiopathic purpura hemorrhagica.* (Case observed in Professor Riehl's clinic, Vienna.)

History.—J. S., man aged 33, postman. Family history unimportant. Scarlet fever at 10; sore throat at 21; no other illnesses. For the four days previous to admission to the hospital the patient had been troubled with epistaxis and had noticed a purpuric rash. History otherwise negative.

Physical Examination.—A well developed and nourished man. Except for fine petechiae scattered over face, body, legs and arms, nothing of importance was disclosed.

Laboratory Examination.—For the platelet count and bleeding time, see Table 3. Coagulation time normal. Clot firm and non-retractile. White count varied from 3,000 to 13,000. Polymorphonuclears 35 to 50 per cent.; remainder lymphocytes with occasional eosinophils and basophils. No blasts. Hgb. 70 to 60 per cent., Sahli. Appearance of reds normal. Urine and stools not remarkable except for the presence of a considerable quantity of blood.

Course of the Disease.—The patient was under observation about one month. During this time there was but little improvement. After the first few days the stools and urine contained only traces of blood. Numbers of fine petechiæ appeared at frequent intervals. Submucous hemorrhages appeared frequently on the tongue, gums and cheeks, and from these would proceed small hemorrhages. Slight epistaxis was present a considerable part of the time. The bleeding time was always prolonged—at some times much more than others. The shortening of the bleeding time and amelioration of hemorrhage bore possibly some relation to variation in the platelet count. Counts, however, at a level of 10,000 are none too accurate, and it is perhaps unsafe to draw conclusions from them.

TABLE 3.—PLATELET COUNT AND BLEEDING TIME IN CASE 4

Date	Platelet Count	Prolonged Bleeding Time	Hemorrhage	Fresh Petechiæ on Skin
February—				
25	Under 1,000	Extreme	Much	Many
27	Under 1,000	Extreme	Much	Many
March—				
1	Under 1,000	30 min.	Much	None
2	4,000	Extreme	Slight	None
3	9,000	7 min.	Slight	None
4	5,000	Moderate	Slight	Mod. number
5	1,000	Extreme	Slight	Mod. number
6	Under 1,000	Extreme	None	Mod. number
10	3,000	Moderate	None	None
11	2,000	Extreme	None	None
13	2,000	Extreme	Slight	None
14	6,000	12 min.	Slight	None
15	9,000	10 min.	Slight	None
16	7,000	8 min.	None	None
17	2,000	Extreme	Slight	Many
18	6,000	7 min.	Slight	None
19	Extreme	Slight	Many
20	Under 1,000	Moderate	Slight	Many

One of the most striking features of the case was the patient's good general condition and freedom from symptoms other than hemorrhage.

CASE 5.—*Epistaxis in a woman with phthisis.* (Case observed in Professor Romberg's clinic, Tübingen.)

History.—K., woman aged 35, housewife. Family and past history negative for hemorrhagic disease. For several months the patient had had symptoms of rather rapidly advancing phthisis. For three days she had had epistaxis. History otherwise unimportant. Physical examination disclosed considerable consolidation at lung apices with possible cavity formation. Nothing further of importance. Daily temperature varied from 37 to 40 C.

Slight epistaxis continued for four days and then ceased. This and the prolonged bleeding time were the only evidences of hemorrhagic diathesis. (For the platelet count and bleeding time see Table 4.)

CASE 6.—*Ecchymoses and epistaxis in a man with aplastic anemia.* (Case observed in Professor Riehl's clinic, Vienna.)

History.—Man, aged 27, clerk. Family and past history negative for hemorrhagic disease. For six months the patient had been troubled with subcutaneous swellings which appeared first on the cheeks and later on the lips and front of the chest. He had been troubled with an occasional slight epistaxis and had noticed a discoloration of the skin over many of the tumors.

TABLE 4.—PLATELET COUNT AND BLEEDING TIME IN CASE 5

Date	Platelet Count	Prolonged Bleeding Time	Epistaxis
May 12	55,000	Moderate	Slight
" 13	50,000	Moderate	Slight
" 15	65,000	Moderate	Slight
" 18	75,000	Slight	None
" 20	80,000	Normal	None
" 23	88,000	Normal	None
" 29	74,000	Normal	None
June 2	130,000	Normal	None
" 12	150,000	Normal	None
" 17	190,000	Normal	None

Physical Examination.—A pale, emaciated man with subcutaneous growths involving mucous membrane of nose and lips, skin of cheeks, chest and abdomen. Over most of the tumors were blue to yellow discolorations of the skin. The tumors were histologically cellular infiltrations of the subcutaneous tissue of unknown character. Physical findings otherwise of no interest in this connection.

Laboratory Findings.—For platelet count and bleeding time see Table 5. White count varied from 7,000 to about 500. Of these 50 per cent. to 90 per cent. were lymphocytes, the remainder polymorphonuclears with an occasional eosinophil and

TABLE 5.—BLOOD FINDINGS IN CASE 6

Date	Platelet Count	Bleeding Time	Leukocytes
Feb. 7	22,500	5 min.	2,000
" 9	19,500	5 min.	below 1,000
" 14	94,500	2 min.	2,500
" 18	177,000	1 min.
" 20	216,000	1 min.	7,000
" 24	180,000	1 min.	3,000
" 27	120,000	1 min.	5,000
Mar. 11	165,000	1 min.	5,500

basophil. No blasts. Red count 3,500,000; Hgb. 50 per cent., Sahli; red count and Hgb. did not vary markedly while the patient was under observation. Reds varied slightly in size and shape. No stippling. The urine and stools contained no blood.

Course of Disease.—During the first few days in the hospital the patient had slight epistaxis, after this, none. The discolorations of the skin began to fade soon after entering the hospital. The blood-picture in this case was of great interest but cannot be dealt with at length in this paper.

CASE 7.—*Chronic purpura hemorrhagica, in a girl with prolapse of the rectum.* (Case observed in the New York Hospital. See Reference 13 for more complete report of case.)

History.—Georgiana, girl, aged 3. One sister was born with a petechial rash; family history otherwise negative. The patient has several times had prolapse of the rectum. Since the age of 19 months she has been subject to nose bleed and ecchymosis on slight injury. On two occasions epistaxis was so severe and prolonged that her life was almost despaired of. On one of these occasions direct transfusion of blood was carried out by Dr. R. D. McClure. Following this there was complete cessation of hemorrhage for three days. On the fourth day she had slight hemorrhage from the nose, vagina and transfusion wounds. On one occasion a fine generalized petechial rash appeared after straining at stool. The patient came under observation once with varicella. Each vesicle was surrounded by a small subcutaneous hemorrhage.

At the time of the one blood examination, the patient was subject to epistaxis and had on her face and body several large ecchymoses. The platelet count was then below 10,000; bleeding time over one hour; coagulation time normal; clot firm and non-retractile.

At the time of another examination, no evidence of hemorrhage could be found. Platelets were then present in abundance. Bleeding time 5 to 10 minutes. Clot retractile.

CASE 8.—*Severe purpura hemorrhagica in child with diphtheria.* (Case observed in Professor Escherich's clinic, Vienna.)

History.—A. E., boy aged 6. Family and past history negative for hemorrhagic disease.

Present Illness.—For several days before admission to the hospital the child had had sore throat. For two days the mother had noticed ecchymoses about the face. For one day he had had epistaxis.

Physical Examination.—The child was extremely toxic and ill. Examination of the throat disclosed a typical diphtheritic membrane. On the face were several ecchymoses, 2 to 4 cm. in diameter.

Laboratory Examination.—Platelet count 3,000; bleeding time extremely prolonged; coagulation time normal; clot firm and non-retractile; white count 75,000.

The patient died two days later. Anatomical diagnosis, pharyngeal diphtheria, toxic myocarditis, toxic nephritis.

CASE 9.—*Chronic purpura hemorrhagica in a woman with gastro-intestinal trouble.* (Case observed in Prof von Noorden's clinic, Vienna.)

History.—J. W., maid aged 37, cook. Family history negative for hemorrhagic disease.

Past History.—Migratory polyarthrititis at age of 18. She has always been subject to attacks of tonsillitis. Since the age of 25 she has had considerable stomach trouble, especially during the summer months. Main complaints were pain, usually at its worst at night, anorexia, nausea and vomiting. She has always been troubled with constipation and has frequently seen mucus in the stools. Never noticed blood in stools nor vomitus.

Present Illness.—Since childhood she has been subject to epistaxis and ecchymosis following slight injury. Since her stomach trouble began this tendency has been much worse, and like the stomach trouble, is at its worst during the summer months. Has for periods had epistaxis, bleeding from the gums, profuse menstruation and has been almost covered with ecchymoses. When patient came under observation hemorrhagic symptoms were mild. Main complaint was stomach trouble, constipation and menorrhagia. Physical examination disclosed nothing of importance except a few small blue and yellow ecchymoses scattered over the body. The uterus was normal in size and position.

Laboratory Examination.—Test meal not remarkable except for slight hyperacidity. Urine and stool not remarkable. Platelet count 9,000. Bleeding time, twelve minutes. Coagulation time five minutes. Clot firm and non-retractile. Leukocytes 9,000. Polymorphonuclears 91 per cent. Lymphocytes 8 per cent. No blasts. Hgb. 90 per cent. S. Reds normal in appearance. One week later the platelet count was as before, 9,000. The bleeding time was eight minutes. There had been no marked change in the symptoms.

CASE 10.—*Few ecchymoses in a man with alcoholic cirrhosis of the liver; chronic interstitial nephritis, secondary anemia.*

The patient, at the time of examination, had several ecchymoses around the knee, which had appeared without adequate cause. No other evidence of hemorrhagic disease.

Platelet count, 50,000. Bleeding time normal.

CASE 11.—*Hematemesis in a man with cirrhosis of the liver.*

At the time of examination the patient was vomiting blood, and had tarry stools. In this case there was no definite evidence of hemorrhagic disease.

Platelet count 60,000. Bleeding time normal.

CASE 12.—*Epistaxis in a man with malignant syphilis.*

The day preceding the blood examination, the patient had had severe epistaxis. No local cause for bleeding found.

Platelet count 65,000. Bleeding time normal.

A few weeks after the above examination the patient had tuberculous peritonitis.

(Cases 10, 11, 12 were observed in Prof. Romberg's clinic, Tübingen.)

CASE 13.—*Severe purpura hemorrhagica in a man with aplastic anemia (proved at autopsy.)* (Case observed in private practice.)

The patient at the time of examination had bleeding from the gums and severe epistaxis. Several large ecchymoses were scattered over the body.

Plates very scarce in fresh and stained blood-preparations. Bleeding time moderately prolonged.

SUMMARY OF CASES

The severer of the cases were examples of purpura hemorrhagica and presented the following symptom complex:

1. Purpura, usually present, conformed to two distinct types—ecchymoses and petechias. The ecchymoses, evidently brought out by mechanical agents such as slight blows, rubbing, etc., presented a varied appearance. In some instances they were simply small bruises, in others large, elevated, indurated, blue to yellow areas over 35 cm. in diameter. Their appearance was dependent partly on the nature of the injury which brought them out, partly on the intensity of the hemorrhagic diathesis. The petechias often developed without local mechanical cause. When such was the case they consisted of small flecks, 1 to 3 mm. in diameter, were more or less uniform in size, had usually a very general, and sometimes an almost universal, distribution. They were observed even on the scalp, soles of the feet, conjunctivae, mucous membrane of the mouth, etc. They were, as a rule, most abundant on the dependent parts and in these localities were frequently confluent, forming flat blue to yellow flecks—1 to 2 cm. in diameter. Petechias, although often appearing without apparent local cause, were not entirely independent of mechanical influence. They were frequently brought out by rubbing, scratching, etc. In

one patient, a fine petechial rash appeared immediately after straining at stool (Case 7). A petechial rash was most commonly observed in patients who were up and about and working, and frequently faded rapidly when they were confined to bed. The latter observations make it seem that changes in capillary blood-pressure play some rôle in the production of this rash.

The appearance of the purpura was modified by the co-existence of other skin lesions and sometimes gave rise to peculiar appearances. For example, in a patient with chicken-pox (Case 7), a small area of purpura surrounded each vesicle. In a patient with acne rosacea (Case 3) each pustule was the site of a small hemorrhage. In a patient who presented numerous peculiar subcutaneous tumors there was a blue to brown discoloration of the skin over each growth (Case 6).

2. The ecchymoses were frequently, and the petechias almost always, accompanied by bleeding from one or more mucous surfaces—in fact, epistaxis, bleeding from the gums, etc., were the symptoms usually first noticed by the patient. Often bleeding proceeded from trivial abrasions of the mucous membranes, sometimes from petechias in the mucous membrane and occasionally oozed from membranes on which no lesion could be discovered.

3. The bleeding time was in all cases prolonged, usually very much so. It exceeded one hour, as a rule, when symptoms were severe, and dropped to normal as soon as the condition was relieved. This is one of the most constant and distinctive features of this disease. It is the consequence of a tendency which these patients have to bleed profusely from every vascular lesion no matter where or how produced. For example, one patient, with a bleeding time exceeding two hours, bled for hours from a hang nail on the thumb, bled profusely from acne lesions on the face; the chewing of coarse food caused the gums to bleed, there was blood in the urine and stools, and the rubbing or scratching of the skin brought out petechias.

4. The platelet count, in all severe cases, was reduced to the point of almost total absence. It did not exceed 10,000 in a single instance, and frequently was so low that platelets could be found neither in stained smears nor in counting chambers. In two instances in which it was believed from the above examinations that platelets were totally absent, the undiluted plasma was studied by Bürker's method²² and the presence of a few platelets demonstrated. As previously stated, the count was always excessively low while the general symptoms were severe. In every case, a rise in the count was accompanied by marked amelioration or complete relief of hemorrhagic diathesis. As a rule, the rise occurred

22. Bürker, K.: Eine einfache Methode zur Gewinnung von Blutplättchen. *Centrabl. f. Physiol.*, June 20, 1903.

spontaneously, but in three cases (Cases 1, 2 and 7) it was evidently the direct result of transfusion. In these cases, the tendency to bleed returned as soon as the count reached the low level which existed prior to transfusion. In one instance (Case 4) platelet counts were made almost daily for a period of twenty-four days. In this case the tendency to bleed was most marked when the count was below 1,000, and amelioration of symptoms was noticeable whenever it rose to 9,000. The percentage of error in counting platelets is greater when the count is extremely low than when it is about normal. It is hardly safe, therefore, to draw conclusions from such slight variations.

5. In every case the coagulation time fell within normal limits. No striking variation in this either with the platelet count or with the severity of hemorrhagic diathesis was noted.

6. The clot was firm in every case.

7. The clot was non-retractile in every case so long as the platelet count was extremely low, and showed more or less retractility as soon as the count rose.

Many of the symptoms just mentioned were lacking in the milder cases; in fact, in these the diagnosis of the condition rested on the finding of a low platelet count. The symptoms most frequently complained of were small ecchymoses and epistaxis. Frequently neither was observed and the possibility that hemorrhagic diathesis existed was suggested simply by the fact that hemorrhage was present and seemed somewhat too severe or prolonged to be entirely accounted for by its local cause. Such hemorrhages were, for example, continued bleeding from intestinal ulcers (Case 2), profuse hemorrhage from esophageal varices (Case 11), profuse and prolonged menstruation (Case 9), etc.

The bleeding time in the milder cases was in some instances normal, and in others slightly or moderately prolonged. The platelet count fell between 19,500 and 60,000. The coagulation time was within normal limits. The clot was firm, and as a rule, gave diminished retractility.

There can be little doubt that the mild and the severe cases, differing as much as they did in hemorrhagic manifestations, are examples of one and the same disease, differing only in degree.

The entire symptomatology of the condition may be summarized by stating that in this disease there exists a tendency to bleed from every vascular lesion, no matter how produced. In severe cases an elevation of capillary blood-pressure by exercise, straining, etc., a rubbing or scratching of the skin, the presence of inflammatory lesions or of minute cuts or other abrasions of the skin are sufficient to produce purpura or prolonged hemorrhage. In mild cases, however, more severe lesions are required to produce the same phenomena. It is extremely interesting to find that a consistent tendency to bleed is not more frequently observed

in the other types of hemorrhagic diathesis. Such is the exception and not the rule. As mentioned, when discussing the bleeding time, we have observed patients with jaundice who bled profusely after operation and yet had a normal bleeding time and no purpura. The same observation was made on a patient with hemophilia. A patient with jaundice, ecchymoses, epistaxis and blood in the urine and stool gave a normal bleeding time. Several patients with purpura simplex who were almost covered with large ecchymoses had no hemorrhage from mucous membranes and would hardly bleed at all when the ear was pricked. All of the patients just mentioned gave high platelet counts.

THEORETICAL CONSIDERATIONS AND EXPERIMENTAL RESULTS

The following facts have led me to believe that an absence of blood-platelets plays an essential rôle in the pathogenesis of the type of purpura hemorrhagica with which we are here dealing:

1. Every case of pathologic hemorrhage observed by me, which presented a certain clinical picture (purpura, bleeding from mucous membranes, a prolonged bleeding time, a normal coagulation time and a firm blood-clot) had enormously reduced platelet counts. The tendency to hemorrhage vanished when the platelet count rose to a certain point, and reappeared when the count fell. The first observation was alike true, whether the rise in the count occurred spontaneously (Cases 3, 4, 5, 6) or was the direct result of transfusion (Case 1, 2 and 7).

2. A large number of platelet counts were made by me in three diseases (diphtheria, tuberculosis and nephritis) in which purpura hemorrhagica of the type here described was thought to be a complication. The typical disease-picture appeared in two instances (Cases 3 and 8) and in only two. In both of these cases the platelet counts were below 3,000. These were the lowest counts found in this series of cases. In a third case (Case 5) the count, for a few days, varied between 55,000 and 65,000. The patient at this time had mild hemorrhagic diathesis (epistaxis and a moderately prolonged bleeding time). Three rather low counts (40,000, 60,000, 75,000) were observed in patients with diphtheria who presented no evidence of hemorrhagic disease. These results with others, which will be reported later, indicate that 40,000 to 75,000 is a level at which patients may or may not have a mild disposition to bleed. A marked reduction below this, however, has been in my experience without exception accompanied by hemorrhagic diathesis.²³

3. Purpura hemorrhagica occurs as a complication in a varied collection of diseases, all of which possess one feature in common—a liability

23. The cases of purpura hemorrhagica reported by Hayem and Helber gave counts (40,000 to 89,000) higher than any observed by me when the estimation was made at a time when bleeding was severe. This variance in results is possibly due to differences in the methods employed for counting.

to reduction in the number of platelets. Hayem and Bensaude^{3, 24} have observed it complicating lymphocytic leukemia, hemorrhagic small-pox and tuberculosis; Pratt⁹ complicating nephritis; Selling¹⁰ complicating aplastic anemia due to benzol poisoning; I have found it complicating diphtheria (Case 8), tuberculosis (Case 3) and aplastic anemia (Case 13). I have also observed it in a more or less severe form in patients suffering from chronic ulcerative colitis (Case 2), prolapsus of the rectum (Case 7), cirrhosis of the liver (Cases 10 and 11) and in a gastrointestinal condition (Case 9), which seemed to be spastic constipation associated with gastric hyperacidity.

4. I have been able to produce severe hemorrhagic diathesis in animals by reducing the platelet count by means of diphtheria toxin and mild hemorrhagic diathesis with benzol. The condition appeared only in the animals in which the platelet count was enormously reduced. It became apparent at the time when the platelets disappeared from the circulation and was relieved when the platelet count rose. These results will be reported in detail in a later paper. One very interesting result was the following:

EXPERIMENTAL PURPURA HEMORRHAGICA

Experiment 34.—Male rabbit, weight 2.5 kg.

Diphtheria toxin given in small doses (June 14 to 17, 1911), until the animal appeared to be somewhat ill. The animal speedily recovered from the effects of the toxin and showed no further untoward symptoms. On June 26th, that is, nine days after the last dose, it was noted for the first time that hemorrhage, resulting from a prick in an ear vein, was almost impossible to check. The bleeding time, obtained by shaving the skin of the back and cutting fairly well through it with a razor, was excessively prolonged. The fortieth drop of blood was almost as large as the first; that is, the flow of blood, after a period of twenty minutes, showed almost no diminution in intensity. The bleeding time, when tested similarly in other animals, was one minute or less, in fact, in many instances the blood would hardly flow spontaneously at all. On the following morning the hair covering the ear and back of the animal was matted with blood and the cage was everywhere splattered with blood. A similar result was noted in no other of thirty-eight experiments. Numerous subcutaneous hemorrhages in the ears were then noted for the first time. This eruption was quite striking. Some of the hemorrhages were about 0.5 cm. in diameter—the majority were petechial, 1 to 3 mm. in size. These were distributed regularly over both ears, being as numerous over the areas which had not been punctured for obtaining blood as over the areas which had been shaved and pricked. No purpura could be found on the surface of the body. Such hemorrhages were seen in none of the other animals. Blood collected in a test tube clotted quickly, but failed to retract and extrude serum even after standing four days. The animal was at this time quite anemic and remained so as long as observations were continued. The hemoglobin was 25 per cent. The white count 16,000. Polymorphonuclear cells 60 per cent. Lymphocytes 40 per cent. No blasts were seen.

The prolonged bleeding time and excessive hemorrhage from pricks in the ear veins continued unchanged for three days; that is, up to June 29. On this date the bleeding time was less prolonged, the twentieth drop was about half the size

24. Bensaude, R., and Rivet, L.: *Purpura hémorragique et tuberculose*. Presse méd., July 25, 1906.

of the first, and the hemorrhage from pricks in the ear veins was less profuse. The platelet count at this time had risen to 64,000 and continued to rise. The following day the bleeding time showed only a slight delay and after that was always normal. The bleeding from pricks in the ear veins was never again profuse. The animal, during the following week displayed no tendency to excessive hemorrhage. The data in detail are given in Table 6.

Except for the absence of epistaxis, this was a perfect experimental reproduction of the purpura hemorrhagica which complicated diphtheria (Case 8). It was evidently the same condition both etiologically and pathogenetically. All of the distinctive features were present; purpura, prolonged bleeding time, an extremely low platelet count, blood which clotted quickly, gave a firm clot, and failed to retract and extrude serum. The disease appeared the day the platelet count dropped to an extremely low level (4,000), persisted as long as the platelet count remained low, and

TABLE 6.—PLATELET COUNT IN THE AUTHOR'S EXPERIMENTAL CASE

Date	Platelet Count	Remarks	Date	Platelet Count	Remarks
June—			June—		
13	430,000	26	4,000	Purpura hemorrhagica
14	620,000	Toxin S C	27	4,000	Purpura hemorrhagica
15	600,000	28	8,000	Purpura hemorrhagica
16	570,000	Toxin S C	29	64,000	Less severe
17	560,000	Toxin S C	30	100,000	Less severe
18	690,000	July—		
19	690,000	1	150,000	Well
20	930,000	2	250,000	Well
21	860,000	Animal Well	3	380,000	Well
22	970,000	Animal Well	4	460,000	Well
23	1,700,000	Animal Well	5	370,000	Well
24	1,040,000	Animal Well	6	Well
25	440,000	Animal Well	7	570,000	

disappeared as soon as the count rose. No tendency to bleed was observed in other animals treated with the same and much larger doses of diphtheria toxin. This, I think, was due to the fact that the platelet count did not fall to such a low level.

In order to prove that an absence of platelets is a cause of hemorrhagic disease, it would be desirable to find the agency through which this might be possible.

Morawitz²⁵ found that platelets contain large amounts of prothrombin (or thrombogen or the antecedent substance of the fibrin ferment). Jones,²⁶ working in Professor Howell's laboratory, confirmed the results of Morawitz, and in addition demonstrated that platelets liberate a throm-

25. Morawitz: Arch. klin. Med., 1904, lxxix, 215. Cited by Jones, Note 26.

26. Jones, S. Bayne: The Presence of Prothrombin and Thromboplastin in the Blood Platelets. Am. Jour. Physiol., 1912, xxx, No. 1.

boplastic substance which he named thromboplastin. These results make it appear remarkable that blood in which platelets can hardly be demonstrated is able to clot both quantitatively and at a normal rate. This is, however, beyond question a fact. Both Denys and Hayem thought so from their microscopic studies of blood films. My studies, which confirm their views, were as follows:

The platelet count in dogs was reduced to about 10 per cent. of normal by repeated injections of benzol. In these cases blood coagulation was carefully studied. The fibrinogen content of the blood was shown to be at the upper limit of normal (0.55 per cent. to 0.65 per cent.). The coagulation time was normal or slightly prolonged. The latter was accounted for by the presence of jaundice. All the fibrinogen present was transformed into fibrin by coagulation—at least the blood-serum obtained, after coagulation, was shown to be free from fibrinogen (the serum, when neutralized and heated to 58 C., gave no precipitate). The results in the human cases were in harmony with the experimental. The coagulation time was about normal—in some cases even shorter than normal—the clot was firm and a microscopic study of the fibrin showed no striking qualitative or quantitative deviation from the normal.

The macroscopic appearance of the clot, noted both in the experimental and in the human cases, differed strikingly from that of normal blood, inasmuch as it failed to retract and extrude serum. Hayem,² the first to observe non-retractility of the blood-clot, performed some very interesting experiments which throw light on its meaning. He collected horse blood, and at a low temperature, threw down the red and white corpuscles by centrifugalization. The supernatant plasma contained an abundance of platelets. From a portion of this, platelets were removed by filtration. Both specimens were then allowed to clot. The portion containing platelets retracted and extruded serum. The filtered portion clotted, but failed to retract. Hayem concluded that platelets give to the clot its property of retractility. It has been observed, however, that under some conditions, blood containing an abundance of platelets, gives a non-retractile clot. The clinical and experimental results on this subject of Hayem, Le Sourde and Pagniez²⁷ and others, may be summarized by saying that the presence of blood-platelets seem indispensable for normal retractility of the blood-clot, but retraction occasionally fails to take place even when platelets are present in abundance.^{2, 27} Le Sourde and Pagniez²⁸ have recently shown that the blood of patients with purpura hemorrhagica gives a retractile clot if a suspension of blood platelets

27. Le Sourde and Pagniez: *Jour. de physiol. et path. gén.*, 1907, ix, No. 4. Cited by Pratt.

28. Le Sourde and Pagniez: *Un cas de Purpura Hemorrhagique avec Disparition totale des Plaquettes du sang.* *Bull. et mém. Soc. méd. d. hôp. de Paris*, July 12, 1912.

is added to it. Whether this interesting but more or less an artificial phenomenon (failure of the clot to retract) is an evidence of an abnormal fibrin formation which could play a part in the pathogeny of hemorrhagic disease, is questionable. It may be due to the fact that platelets are not present to anchor together the filaments of fibrin; or it may be comparable to the failure of the milk clot to retract. This happens if rennet is added to it in insufficient amount.²⁹

Hayem produced a condition of the blood which both Denys¹ and he^{3, 30} considered analogous to purpura hemorrhagica. He injected blood-serum of one animal into the circulation of an animal of different species. The platelets began immediately to stick together and finally formed clumps so large that they were to a great extent filtered off from the circulating blood by the capillaries. He states that a similar condition follows the injection of rattlesnake venom in animals. This was considered by Denys and Hayem to be the pathogenesis of purpura hemorrhagica. They suggested that multiple platelet emboli could account for the purpura, and abnormal coagulation for the hemorrhage. This ingenious and attractive theory explains, perhaps, some types of hemorrhagic diathesis. I am, however, unable to reconcile it with all the data obtained in my studies and at present believe that the type of disease described in this paper has a totally different cause. It is not desirable at present to discuss this question at length, for experimental purpura hemorrhagica produced by the injection of diphtheria toxin offers such an admirable opportunity for further study. This condition we are safe in assuming is exactly the same as that observed in humans. It may be permissible, however, to mention briefly several observations which I cannot reconcile with the theory of Denys and Hayem.

1. Following the intravenous injection of peptone into animals, a condition results which is analogous to that produced by Hayem with animal serum. The platelets clump together and are to a large extent filtered off from the circulating blood. Such blood withdrawn in a blood-pipet and diluted (1-100) with Wright and Kinnicutt's solution or a 4 per cent. aqueous solution of sodium metaphosphate, gives a striking picture. The red cells are laked and the platelets are clumped into masses of from several to several hundred. Such a condition as this was not observed in the study of my human or experimental cases: Even in Experiment 34, when 1,700,000 platelets per mm. of blood disappeared from the circulation within three days, no tendency to clumping was observed.

2. In Case 7 a petechial rash appeared immediately after straining at stool. This certainly suggests a wide-spread capillary rupture as the cause

29. R. Bräuler: Der Einfluss verschiedener Labmengen und verschiedener Temperaturen auf die Gerinnung der Milch und auf die mikroskopische Struktur der Kasein und Fibringerinnsel. Arch. f. ges. Phys., 1910, cxxxi, 519.

30. Hayem, G.: Leçons sur les maladies du sang. Masson, 1900, p. 586.

of purpura, not platelet emboli. Other facts might be mentioned in support of this. For instance, purpura was often brought out by blows, rubbing, etc. Petechias were most abundant on the dependent parts when the patients were up and about, and often disappeared completely when they were confined to bed.

3. In Case 4 the platelet count was below 10,000 for a period of nearly a month. During this time great numbers of petechias appeared, and at this time there were scarcely enough platelets present to produce a sufficient number of emboli to account for them.

4. In Case 1, the purpura faded rapidly after transfusion and did not reappear as the platelets introduced by transfusion vanished. If the disappearance of these platelets was the result of clumping and embolism, the purpura should have been increased instead of decreased by transfusion.

Hemorrhagic diathesis of this type can be accounted for theoretically best, I believe, as follows: It is well known that hemorrhage is not stopped by a clot, such as is seen on the surface of wounds, but chiefly by intravascular plugs (thrombi). A clot and a thrombus have totally different architectures and modes of formation. A clot is formed from blood at rest, and consists of a homogeneous mixture of platelets, red cells, leukocytes, fibrin, etc. Without question, the coagulation of fibrinogen plays the essential rôle in this process. It takes place at about the normal rate, and quantitatively whether platelets are present or not. A thrombus, however, is a different matter. It is formed from blood which is flowing, and we have reason to believe that for its formation a certain number of platelets is indispensable. Platelets, from the property they possess of sticking to injured tissue and then to each other, adhere to any injured point in a blood-vessel and are deposited there in enormous numbers by the blood as it flows past.³¹ This is the beginning of the process which plugs a bleeding vessel. Later, fibrin, leukocytes and red cells are deposited and, finally, thrombosis is complete. Judging from the experimental results, platelets not only initiate, but also make up a large part of the bulk of a completed thrombus. It is easily conceivable that an almost complete absence of platelets from the blood should lead to abnormality in the initiation or completion of thrombosis, and be a cause of prolonged hemorrhage, whether the fibrin-forming elements were normal or not. The fact that a patient bleeds for an hour or more from a pin prick or a mere scratch is abundant evidence that in that patient thrombi fail to form, and since an absence of blood

31. Hayem, G.: (a) *Recherches sur l'anémie norm. et path. du sang*, Paris, 1878; (b) *Compt. rend. Acad. des sc.*, July 18, 1882; (c) Bizzozero: *Virchows Arch. f. path. Anat.*, 1882, xc, 261. (4) Eberth and Schimmellbusch: *Virchows Arch. f. path. Anat.*, 1885, ci, 1886, ciii, cv. The foregoing cited by Welch. (e) Welch, William H.: *The Structure of White Thrombi*, Tr. Path. Soc. Philadelphia, 1887, xiii.

platelets is constantly accompanied by this phenomenon, it seems evident that the rôle played by platelets in thrombus formation is an essential one. I have studied experimental thrombi by the methods used by Professor Welch in rabbits in which the platelet count was reduced to as low as 60,000 by subcutaneous injections of benzol. Thrombi formed in such animals. They seemed smaller than normal, but contained, as do normal thrombi, great numbers of agglutinated platelets and leukocytes, and also fibrin and red cells. These results harmonized with the fact that these particular animals displayed no striking tendency to bleed abnormally long. We have not yet studied thrombus formation in the more extreme cases in which platelets are almost totally absent from the blood and hemorrhage is excessive.

An absence of platelets perhaps accounts for the tendency to bleed from cuts. The explanation of the purpura, however, is not so clear. My evidence suggests that both forms of purpura (both the fine petechias and the ecchymoses) are due to hemorrhage from ruptured blood-vessels, and not to thrombosis nor platelet emboli. Whether or not the vessels in this disease are abnormally friable is difficult to say. It is possible that in healthy individuals, under the usual conditions of life, a few capillaries are continually rupturing, and that the minute ruptures are immediately closed by the adherence of a few platelets and a few filaments of fibrin. When the tendency to bleed is pathologically enormously increased, it is possible that such ruptures lead to visible hemorrhages which appear as fine petechias. Bruising, rubbing, etc., would cause a number of ruptures in a small area and lead to the formation of the larger hemorrhages — the ecchymoses. This explanation seems in accordance with facts as I now understand them. It explains, I believe, the fine petechias and the traumatic ecchymoses of the platelet free type of disease. It is not believed, however, that it would account for the larger purpuric flecks seen in other types of hemorrhagic disease, which appear without local causes.

As to etiology, it may be said that any agent which lowers the platelet count to a point of almost complete absence would appear to be a cause of purpura hemorrhagica. Purpura hemorrhagica of this type, would seem to be then, a symptom, not a disease. Severe cases have been observed complicating lymphocytic leukemia, hemorrhagic small-pox, tuberculosis, nephritis, aplastic anemia, benzol poisoning, diphtheria and gastro-intestinal conditions. Further study will undoubtedly add to this list. A minority of the cases develop in individuals who seem otherwise healthy.

SUMMARY AND CONCLUSIONS

1. By comparing symptoms and blood findings in all patients observed during a period of three years, who displayed a pathologic tendency to bleed, it has been possible to pick out a certain group of cases which

presents a characteristic clinical picture, which is due wholly or in part, it is believed, to an enormous reduction in the number of blood-platelets.

The disease in its severer form almost constantly presents the following symptom-complex: 1. Purpura of one or two types—petechias or ecchymoses. 2. Hemorrhage from mucous membranes. 3. A tendency to bleed from every vascular lesion, no matter how produced. In consequence of this tendency, the bleeding time is very greatly prolonged, often exceeding two hours. 4. A normal coagulation time. 5. A firm blood-clot. 6. In consequence of the absence of platelets, a clot which does not retract and extrude serum. In all cases (seven) seen by me showing the above picture, the number of platelets was reduced almost to a point of absence. Counts were all below 10,000, and as a rule, below 1,000. (The normal platelet count varies from 200,000 to 400,000.)

The disease in its milder form presents a different picture. The most common symptoms in the milder cases are ecchymoses following slight injury and epistaxis. Sometimes neither purpura nor bleeding from normal mucous membranes appears and the only evidence of hemorrhagic diathesis is severe hemorrhage accounted for to a greater or less extent by local causes; for example, continued bleeding from intestinal ulcers, from esophageal varices, profuse and prolonged menstruation, etc. The bleeding time in the mild cases is sometimes normal and sometimes slightly or moderately prolonged. The coagulation time is normal, the clot firm, retractility diminished. The diagnosis rests on the finding of a reduced platelet count. It varied, in my cases (six), from 20,000 to 65,000.

2. Hemorrhagic diathesis can be followed best in this disease by determining the bleeding time at frequent intervals. The simple observation of purpura, spontaneous hemorrhage, etc., may lead to false conclusions in regard to the general condition, for these symptoms are often due to general and local causes combined.

3. When there was opportunity to make such observations it was noted that the disease appeared when the platelet count fell to an extremely low level, persisted so long as the count remained low and disappeared as soon as the count rose.

4. The disease was relieved immediately in two cases by direct transfusion of blood. The relief was coincident with an increase in the platelet count, evidently a direct result of the transfusion. Symptoms returned when the platelet count fell again.

5. The disease was produced in rabbits by reducing the platelet count with diphtheria toxin. The disease appeared the day the platelet count descended to a point of almost complete absence and persisted until the platelet count rose. Hemorrhagic diathesis in mild form was brought

about with repeated injections of benzol. In the latter experiments the count did not descend to such a low level as in the former.

6. In a series of thirty-eight animal experiments,³² in which the platelet count was enormously changed with subcutaneous injections of benzol, diphtheria toxin and tuberculin, and also in a large series of cases in humans in which routine platelet counts were made, only those having extremely low counts gave the complete symptom-complex described above. Several platelet counts between 40,000 and 75,000 were observed in patients who had no marked tendency to bleed. This seems to be the level at which patients may or may not have an abnormal tendency to bleed. No counts lower than these were observed in patients not subject to hemorrhage.

7. The disease has been observed complicating a varied set of diseases — in severe form in lymphocytic leukemia, hemorrhagic small-pox, tuberculosis, nephritis, benzol poisoning, aplastic anemia and diphtheria. The one feature in common in these cases was the low platelet count and the modification of the clot dependent on it; i. e., absence of retractility. Purpura hemorrhagica of the type described would seem, therefore, a symptom, not a disease. It is caused apparently by any agent which reduces the platelet count to a sufficient degree.

In conclusion I wish to express my thanks to Drs. W. W. Gannett, F. C. Shattuck, F. T. Murphy and Hugh Cabot of the Massachusetts General Hospital, to Dr. L. A. Conner of the New York Hospital, to privatdoctents von Jagie of the von Noorden clinic, Kren of the Riehl clinic and Schick of the Escherich clinic in Vienna, and to Professor von Romberg of the Medical clinic in Tübingen for the privileges granted in their wards and laboratories while this study was being completed; also to Drs. J. H. Wright and Roger Kinnicutt of the Massachusetts General Hospital for the use of their excellent method for counting platelets, and to Dr. G. H. Whipple of the Hunterian Laboratory for Experimental Pathology of the Johns Hopkins Hospital for the privilege of working in his laboratory and for suggestions regarding fibrinogen analysis.

Rialto Building.

32. Duke, W. W.: Paper not yet published.

THE WASSERMANN TEST IN THE TROPICS

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Probably every physician who performs the Wassermann test adopts certain minor variations in technic, which tend to make the test more satisfactory in his hands. It is always interesting and instructive to learn the writer's technic before reading his results. The Noguchi modification¹ of the test has been used in the board of health laboratory at Ancon because it is one of the most accurate complement deviation tests for syphilis, because every reagent may be titrated separately and standardized, and because there is always abundant opportunity for obtaining human blood.

TECHNIC

Corpuscle Suspension.—A little over 1 c.c. of human blood is taken in 9 c.c. of a solution containing 0.9 per cent. salt and 1.5 per cent. sodium citrate. The corpuscles are washed three times with normal salt solution and then centrifugalized for measurement. As 1 c.c. of blood contains approximately 0.4 c.c. of corpuscles, the blood is taken into a graduated centrifuge tube and after washing, 0.4 c.c. of corpuscles are suspended in 10 c.c. of normal salt solution to obtain a 10 per cent. suspension. This method of measurement is easy and gives a constant suspension.

Hemolytic Amboceptor.—The amboceptor is prepared in the manner advocated by Noguchi. The amboceptor unit determined by the use of an overwhelming amount of complement has not been a satisfactory unit for practical purposes in my hands. Instead I have determined the amboceptor unit by the following method described by Noguchi: To a series of tubes each containing 1 c.c. of a 1 per cent. suspension of human corpuscles and 0.02 c.c. of mixed guinea-pig serum is added a varying amount of amboceptor; the amount which causes complete hemolysis in two hours is considered one unit.

Complement.—The complement consists of the mixed sera from several guinea-pigs. This is never over twenty-four hours old at the time of use. The blood is obtained by aspirating the heart under aseptic precautions with a 10 c.c. Luer syringe. An anesthetic is always employed. The same pigs are used repeatedly. There are twelve small pens set aside for the "Wassermann" pigs; the test is performed twice a week; thus each pig is bled about once every six weeks. The entire lot is changed about once in six months. The relative amount of complement in the serum does not seem to be affected by bleedings of this frequency. The amount of complement required with one unit of amboceptor to cause complete hemolysis of 1 c.c. of a 1 per cent. suspension of corpuscles is considered one unit. The test is performed with two units of amboceptor and two units of complement. For over a year a preliminary titration of the complement, as recommended by Craig,² has been made before performing the test.

*Manuscript submitted for publication July 18, 1912.

1. Noguchi, H.: Serum Diagnosis of Syphilis. J. B. Lippincott, Phila., 1910.

2. Craig, Charles F.: Further Observations on the Complement Fixation Test in the Diagnosis of Lues in the Military Service. Jour. Infect. Dis., 1911, ix, 216.

Antigen.—Alcoholic extracts of human livers and the acetone insoluble fraction of alcoholic extracts have been used as antigens and one has proved no more stable than the other, but this may be due to the fact that the latter were not kept hermetically sealed. Four or five antigen units have been employed in the performance of the test with but few exceptions.

Patient's Serum.—The blood is aspirated from a vein at the bend of the elbow, allowed to clot or centrifugalized, if necessary, and the serum pipetted off into sterile lysis tubes. These are kept in the ice-box until needed for use. The sera are then heated to 56 C. for twenty minutes and 0.08 c.c. of each serum is added to each of two tubes, the test-tube and the control-tube.

Mixture of Reagents.—The method of using papers impregnated with reagents has not been adopted as it seemed fully as accurate and much easier to mix several of the reagents in bulk, always mixing a larger amount than actually needed. For instance, on a morning when there are thirty tests to be made, two beakers of 40 c.c. each are prepared.

Beaker I		Beaker II	
R. B. C. 10 per cent.	4 c.c.	R. B. C. 10 per cent.	4 c.c.
Mixed complement	80 units	Mixed complement	80 units
Antigen	0	Antigen	200 units
Normal salt sol., q. s.	40 c.c.	Normal salt sol., q. s.	40 c.c.

Then 1 c.c. from Beaker I is added to each even numbered tube containing 0.08 c.c. of serum to be tested and 1 c.c. from Beaker II to each odd numbered tube containing 0.08 c.c. of serum to be tested. From this point on the test is performed exactly as described by Noguchi.

HEMOLYSIN OR HEMOLYTIC AMBOCEPTOR IN GUINEA-PIG SERUM

On several occasions serious difficulty has been experienced by the exhibition of complete hemolysis in all positive control tubes as well as in all the negative control tubes. On the day following each of these mishaps it was noticed that the surplus left in the beakers had completely hemolyzed while a suspension of the same corpuscles in normal salt solution alone showed little or no hemolysis.

TABLE 1.—DEMONSTRATING THE PRESENCE OF A THERMOSTABILE ANTIHUMAN HEMOLYSIN IN GUINEA-PIG SERUM

1. R.B.C.*					= N.H.
2. R.B.C. + G.P.S.** (normal)	0.20				= N.H.
3. R.B.C. +	0	+ G.P.S. No. 100	inact.	0.05	= N.H.
4. R.B.C. + G.P.S. (normal)	0.05	+ G.P.S. No. 100	inact.	0.05	= C.H. 2 hrs.

*R.B.C.—One c.c. of a 1 per cent. saline suspension of washed human red corpuscles.

**G.P.S.—Guinea-pig serum. N.H.—No hemolysis. C.H.—Complete hemolysis.

TABLE 2.—THERMOSTABILE ANTIHUMAN HEMOLYSIN IN GUINEA-PIG SERUM

1. R.B.C.					= N.H.
2. R.B.C. + G.P.S. (normal)	0.20				= N.H.
3. R.B.C. +	0	+ G.P.S. No. 102	inact.	0.10	= N.H.
4. R.B.C. + G.P.S. (normal)	0.05	+ G.P.S. No. 102	inact.	0.02	= C.H. 1 hr.

Suspecting from this that the guinea-pig serum might be the source of the trouble, specimens of their sera were inactivated and titrated for hemolytic amboceptor. Two pigs were detected, 0.05 c.c. of whose serum contained at least one amboceptor unit; many others were detected and

isolated, 0.20 c.c. of whose serum would completely hemolyze 1 c.c. of a 1 per cent. suspension of human red blood corpuscles.

That these sera contained a true thermostabile antihuman hemolysin or amboceptor may be readily seen by Tables 1 and 2.

These pigs had been living in the laboratory court-yard for several generations — about four years — and had been fed on a diet consisting exclusively of tropical grasses.

The sera of another lot of guinea-pigs which had been on the isthmus but a short time was similarly tested. The sera from these pigs in most instances had no effect on human red blood corpuscles even if mixed in equal volumes, and in no instance was hemolysis seen with the use of less than 0.30 c.c. of serum to 1 c.c. of a 1 per cent. corpuscle suspension.

Since this episode we have run a control test tube with each pig's serum before mixing their sera for use in the test. This tube contains 1 c.c. of a 1 per cent. suspension of red blood corpuscles and 0.20 c.c. of the guinea-pig's serum. It is incubated for one hour at 37 C., usually from 4 to 5 p. m., and then allowed to stand at room temperature over night. This test has more than once justified its adoption as a routine procedure.

MALARIA

Were malarial fever, malarial infection or relative malarial immunity to give a positive Wassermann test, or to interfere with any of the reactions taking place in the complement deviation test for syphilis, it would most seriously lessen the value of the test in the tropics or other malarial regions.

TABLE 3.—RELATION OF MALARIA AND THE WASSERMANN REACTION

Patients infected with malarial parasites on the day of admission and having blood taken for Wassermann on the same day.....	15
Wassermann tests negative	12
Wassermann tests positive	3

These three positive cases were as follows:

Periostitis of tibia	1
Syphilitic arthritis	1
Good history of syphilis	1

Of these fifteen infections there were twelve tertio autumnal and three of the tertian form.

TABLE 4.—RELATION OF MALARIA AND THE WASSERMANN REACTION

Patients infected with malarial parasites on the day of admission and having blood taken for Wassermann in from one to four days later.....	84
Wassermann tests negative	68
Wassermann tests positive	16

Of these sixteen positives there were:

Typical secondaries	5
Others with characteristic or suspicious lesions.....	8
Insufficient data	3

Of these eighty-four there were 69 E. A., 2 E. A. and tertian, 9 tertian, and 4 quartan.

TABLE 5.—RELATION OF MALARIA AND THE WASSERMANN REACTION

Patients infected with malarial parasites on the day of admission and having blood taken for Wassermann on average of five to ten days later.....	65
Wassermann tests negative	47
Wassermann tests positive	18

Of these eighteen positives there were:

Typical secondaries	2
Others with characteristic or suspicious lesions.....	12
Insufficient data	4

Of these sixty-five there were 56 E. A., 1 E. A. and tertian, and 8 tertian.

TABLE 6.—RECAPITULATION AS TO MALARIA AND THE WASSERMANN REACTION

Wassermann tests on cases of malaria.....	164
Wassermann tests negative	127
Wassermann tests positive	37

Of these thirty-seven positives, thirty were clinically considered complicated with syphilis.

During the dry season in the Canal Zone 10 per cent. of the laborers, at work and without symptoms, and 30 per cent. of their families, were found by Dr. S. T. Darling³ to be infected with malarial parasites. If this number can be demonstrated undoubtedly a much greater number are carrying malarial parasites, their antibodies or both.

One hundred and sixty-four cases of the 2,846 here considered exhibited malarial parasites at some time during the admission period in which their blood was taken for the Wassermann test. These cases covered a period of nineteen months. Thirty-seven of these 164 gave positive reactions. The great majority of the thirty-seven showed indisputable evidences of syphilis, or gave histories or presented lesions which rendered a diagnosis of past syphilitic infection highly probable. In seven I was unable to collect satisfactory data in reviewing the cases. Many of those giving negative reactions presented nothing in histories or physical signs directly suggestive of syphilis, and a few were purposely taken as controls.

LEPROSY

The Wassermann test was performed on forty-two cases of leprosy; sixteen, or 38 per cent., gave strong positive reactions, and four others gave weak positives, making a total of 47 per cent. positive. All of these were clinically well marked cases, some very much advanced. Some of the most advanced cases gave negative reactions. Whether any of these cases were complicated with syphilis or not we had no means of deter-

3.—Darling, S. T.: Transmission of Malarial Fever in the Canal Zone by Anopheles Mosquitoes. Jour. Am. Med. Assn., 1909, liii, 2051.

mining, for the leprous lesions were such as to obscure a clinical diagnosis of syphilis and such histories as could be obtained were of but little value. Probably a similar condition exists in most leproseria, and if such is the case the influence of uncomplicated leprosy on the Wassermann reaction is a problem which remains to be solved.

Twelve of our forty-two patients were under 20 years of age. Nine of these gave negative reactions, two gave weakly positive reactions and one gave a strongly positive reaction.

Since performing these tests Noguchi's article entitled "Experimental Research in Syphilis"⁴ has appeared, and in this article he states that the serum from each of three lepers gave a negative reaction when a culture of *Treponema pallidum* was used as antigen.

When opportunity is afforded, the forty-two cases above cited will be again tested using the two types of antigen simultaneously.

YELLOW FEVER

The test was performed with the serum of one patient who had had yellow fever and with the serum of one during the attack. Both tests were negative. The latter was seen at the Culebra Island Quarantine Station on about the sixth day of the disease. His temperature had just dropped to 98.6 F.; his pulse was 40. There was an icteric tint to the skin. His urine was brownish-yellow and became solid on boiling. The patient was intelligent and gave a straight-forward history admitting gonorrhea and denying syphilis. There was no evidence of either past or present syphilitic infection. The serum separated from the clot without any hemolysis taking place and was mahogany brown in color. The Noguchi test was performed with 0.02 c.c. of active serum, with 0.08 c.c. of inactivated serum, and with 0.16 c.c. of inactivated serum. There was no inhibition of hemolysis in any instance.

On account of its possible bearing in this connection I wish to allude to the effect of bile or bile constituents on the reaction. It has been stated that if they be present in a blood-serum, such serum will give a positive reaction even though syphilis may be absolutely excluded, and that if bile be added to a normal serum it will also give a positive reaction.⁵ (It must be borne in mind that these statements referred to the original Wassermann test while this paper deals with the Noguchi modification only.) It was possible to confirm this latter statement in a

4. Noguchi, H.: Experimental Research in Syphilis. Jour. Am. Med. Assn., 1912, lviii, 1163.

5. Kaplan, D. M.: The Theoretical Consideration of the Wassermann Reaction and its Practical Application. Am. Jour. Med. Sc., July, 1910.

measure by the addition of varying amounts of highly diluted bile to normal serum. However, the results obtained with naturally jaundiced sera were satisfactory.

In the series of tests considered in this paper the sera were moderately or deeply jaundiced in ten instances. Nine of these sera gave negative reactions. Hemolysis took place as quickly and was as complete with these sera as with other normal sera which were examined at the same time. The jaundiced serum which gave a positive reaction did not inhibit hemolysis in the control tube, a phenomenon which may occur when bile is added to normal serum.

BLACKWATER FEVER

Blackwater fever causes a hematogenous jaundice and the blood serum is mahogany-brown in color. Each of four cases gave a negative Wassermann test.

YAWS

Two cases of yaws in each of which *Treponema pertenuis* was demonstrated and in which there was no history of syphilis and no lesions resembling syphilids other than the typical yaw rupia and the general glandular enlargement, gave positive reactions. A third and similar case gave a negative reaction on two occasions.

FILARIASIS

The reactions in the two cases of filariais (*F. bancrofti*) of long standing were negative. Both of these patients exhibited filarial embryos in the blood-stream at night and both passed chylous urine containing the filarial embryos. The second patient, a white man, claims that he was treated for the same condition in British Guiana in 1904.

AMEBIC DYSENTERY

Five cases of amebic dysentery gave negative reactions. Four of these cases were due to *Entamoeba histolytica*, and one had a heavy infection of *Entamoeba tetragena*.

ARTHRITIS

Tertiary syphilis is seldom held responsible for joint lesions by clinicians.

If a positive Wassermann test coupled with a positive therapeutic test may be taken as a criterion of diagnosis, syphilis plays a most important part in the causation of arthritis.

More than 40 per cent. of the cases of arthritis on which Wassermann reactions were requested during the past eighteen months have given positive tests. This percentage would be still higher if those cases in which a tentative diagnosis of gonorrheal arthritis might have been made were excluded.

The arthritides were characterized by the cardinal signs of inflammation, heat, pain, aggravated by motion or pressure, and swelling. Many of these joints were simply boggy, some had effusion. These lesions were almost always multiple.

The physicians in the medical wards of Ancon Hospital requested the Wassermann test on this class of cases, and to them belongs the credit for suspecting the possibility of syphilis. I present them here to call attention to the value of the test in cases of arthritis.

Out of 100 cases of arthritis, some without other discernible lesions of syphilis and some with one or more tertiary manifestations of the disease, all secondary stage cases being excluded, forty-one, or 41 per cent., gave positive Wassermann reactions.

In a recent number of *Deutsche medizinische Wochenschrift*, Bering⁶ describes a series of eleven cases of arthritis, seven of them not presenting any lesion of syphilis other than the joint lesions, and ten of them giving positive Wassermann reactions.

AUTOPSIES

The Wassermann test is a reaction of value in a certain number of cases which come to the post-mortem table. As time goes on, its value will probably become more and more appreciated. If the blood is recovered shortly after death it is apparently as serviceable as if obtained during life. If post-mortem changes have occurred there is an inhibition of hemolysis in the control tube. Swift⁷ compared the Wassermann test and the Noguchi modification of the same with blood from autopsies in 1909, and a limited use of the test has been made since then.

Below are given some of our cases tested and the results of the tests:

Autopsy 2878	Man, aneurysm ruptured into pericardium; positive.
Autopsy 2991	Man, gumma (?) of heart; positive.
Autopsy 2994	Woman, extensive carcinomatosis; negative.
Autopsy 3030	Man, myocarditis; negative.
Autopsy 3032	Man, aneurysm, ruptured; positive.
Autopsy 3046	Child, malaria, lymphatism; negative.

CONCLUSIONS

1. Guinea-pig serum must be tested for native antihuman hemolysin in certain localities and all sera in which they are found discarded.

2. Malarial infection does not affect the Wassermann reaction (Noguchi modification).

3. Our cases of filariasis, yellow fever, blackwater fever and amebic dysentery all gave negative reactions. Their number is too small to draw conclusions from.

6. Bering, F.: Acquired Syphilitic Joint Disease. *Deutsch. med. Wchnschr.*, 1912, xxxviii, 393.

7. Swift, Homer F.: A Comparative Study of Serum Diagnosis in Syphilis. *THE ARCHIVES INT. MED.*, 1909, iv, 377.

4. Two out of three uncomplicated cases of yaws gave positive reactions.

5. The Wassermann test is of great value in cases of arthritis of uncertain etiology.

6. The Wassermann test should be made an aid to the pathologist in a considerable number of autopsies.

I here wish to express thanks to Col. John L. Phillips, U.S.A., Acting Chief Sanitary Officer, Isthmian Canal Commission, for permission to publish this paper.

I also wish to express thanks to Dr. S. T. Darling, Chief of Laboratory, Ancon Hospital, for helpful suggestions given during preparation of this paper.

POISONING BY NITRIC OXID FUMES *

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This case of fatal poisoning by nitrogen tetroxid fumes is reported for its medicolegal interest and also because of the rarity of the condition and a general lack of recognition of the pathological changes in the lungs of persons dying from the action of this very dangerous gas.

When nitric acid acts on certain metals, such as copper, silver, or cadmium, a gas is given off with the composition of NO or nitrogen dioxide. When this gas comes in contact with the air it absorbs oxygen, with the production of nitrogen tetroxid or N_2O_4 . If either of these compounds of nitrogen and oxygen comes in contact with moisture, nitrogen dioxide forms nitric acid, while nitrogen tetroxid is slowly decomposed into nitric and nitrous acids. These are the decompositions which occur when brown fumes are given off by the action of nitric acid on the substances mentioned above.

When strong nitric acid acts on organic bodies it produces nitrogen trioxid. This immediately decomposes, however, into a mixture of nitrogen trioxid and nitrogen tetroxid. The nitrogen trioxid is continuously converted into nitrogen tetroxid by the action of the atmospheric air. Inhalation of these gaseous compounds occasionally occurs in laboratories or factories where considerable quantities of these fumes are formed, either during the course of some reaction or when a carboy of nitric acid is spilled.

The inhalation of nitrogen tetroxid vapor, if not too concentrated, causes at first no symptoms, with the exception of a slight tendency to cough and an acid taste in the mouth. It has occasionally been observed that workmen have remained for some hours in a room in which nitric acid has been spilled without showing any evidences of injury, or that if on feeling uncomfortable they went into the open air, the symptoms have disappeared rapidly, only to recur in full force six to eight hours later. If the vapors are concentrated, the patient may suffer immediately from severe dyspnea, a feeling of pressure on the chest, coughing, faintness and cyanosis. Dyspnea and slight cyanosis are the frequent symptoms; the patient often on reaching the air also vomits any food that may be in the stomach and then feels perfectly well for a period of six or eight hours. At the end of this time, often without any inciting cause, some-

* Manuscript submitted for publication Aug. 31, 1912.

times while the patient is quietly seated or asleep in bed, there is a sudden attack of extreme dyspnea, with a sense of oppression in the chest, or a feeling of anxiety, so that the cases resemble acute attacks of asthma. Usually there is a good deal of thirst and a sense of suffocation. A cold sweat breaks out on the features, the eyes protrude, and the patient talks with difficulty. From time to time paroxysms of coughing occur, lasting from ten to fifteen minutes and terminating in vomiting. Cyanosis is regularly present. The mind is perfectly clear. The patient usually dies within forty-eight hours, though in some cases death has not occurred for five to eight days, or more rarely two to three weeks.

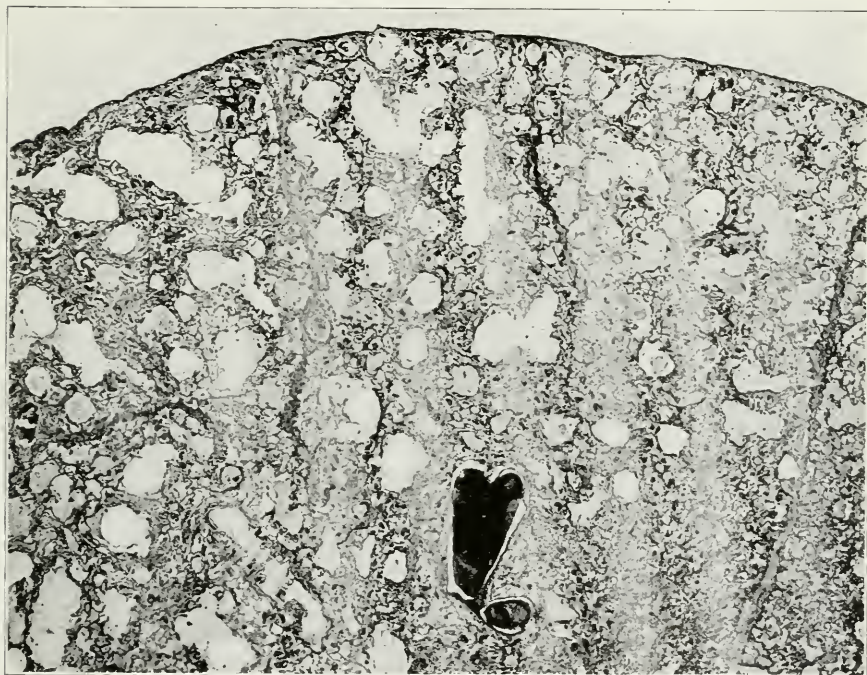


Fig. 1.—Case D. Low power of lung to show irregular distribution of pneumonia and emphysema and thrombi in vessels. $\times 10$.

The blood is dark in color, but generally shows only oxyhemoglobin.¹ The urine may show albumin and blood pigment (in one case, hematin), but not constantly. Death occurs in consequence of edema of the lungs, and is usually preceded by the expectoration of a good deal of foamy yellowish fluid and evidence of cardiac failure. In some cases severe diarrhea and collapse are observed, but this is not a frequent form of termination.

1. Czaplewski was able to demonstrate methemoglobin in only one out of twelve cases of severe poisoning, and this was not a fatal case.

In patients who have inhaled small amounts of gas and have improved after the first attack of edema of the lungs, the disease may continue for a number of days with the clinical symptoms of acute bronchitis and evidences in the chest of lobular or lobar pneumonia. Usually there is extreme dyspnea. The sputum is tenacious, yellowish or brown. Vomiting may be so extreme as to mask the pulmonary symptoms, though as a rule this is uncommon. Such cases may recover, but often show an increased liability to bronchitis or pneumonia for months afterward.

At autopsy the larynx, trachea and bronchi are congested and of a reddish or brownish color. If the patient dies shortly after exposure, the

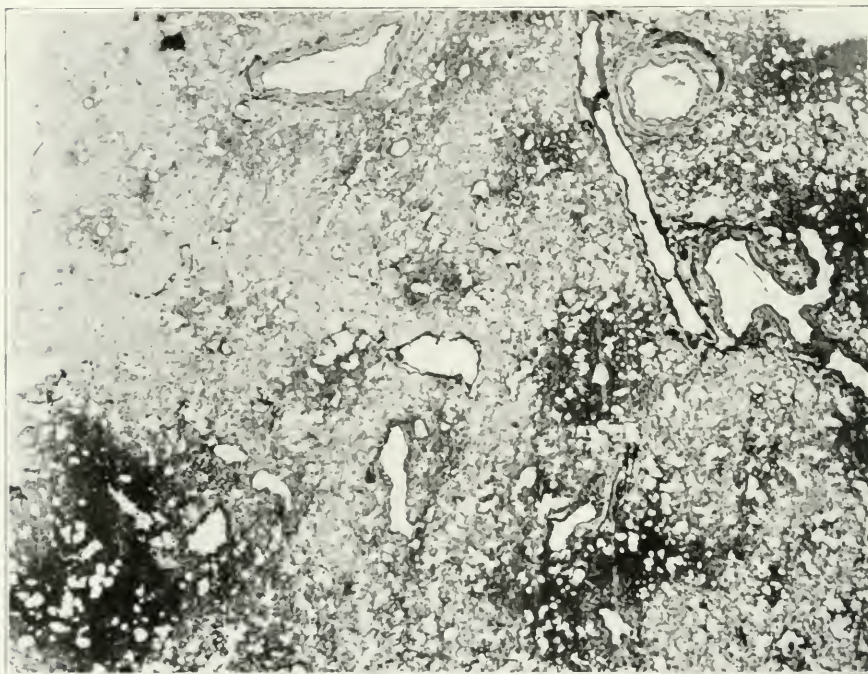


Fig. 2.—Dog 4. Lobular pneumonia with emphysema five days after inhalation of gas. Low power.

lung is edematous; in those living for several days, it is emphysematous, with, in addition, a moderate amount of pneumonic exudate. The vessels of the lung often contain thrombi. From the cut surface exudes a reddish or brownish fluid. In the other organs ecchymoses are occasionally found. Focal necroses may occur in the liver. The meninges are often congested and there are occasionally punctate hemorrhages throughout the substance of the brain. The kidneys have in a few cases shown acute degeneration or acute nephritis; generally, however, they are not much altered.

The number of published cases of death following the inhalation of vapors of nitrogen tetroxid is not very large; but owing to the greatly increased use of nitric acid in the arts, cases of such poisoning are likely to be more frequent in the future, and they may also assume a medico-legal importance in connection with accident insurance and employers' liability acts. On this account the following fatal case is reported, together with the results of animal experiments and a survey of the cases already published.

CASE REPORT

History.—The patient, D., in this instance, accidentally inhaled the fumes arising from a large vessel containing considerable quantities of nitric acid and a cadmium-silver alloy. The room in which the experiment was conducted was small, and the patient experienced some discomfort and a sensation of choking, and went into the open air. After a few minutes he vomited and then felt much better. There were no further symptoms until some six or eight hours later, when he was seized with intense dyspnea, and collapsed. Twenty-four hours later he entered the hospital, remaining there until his death seven days after the exposure.

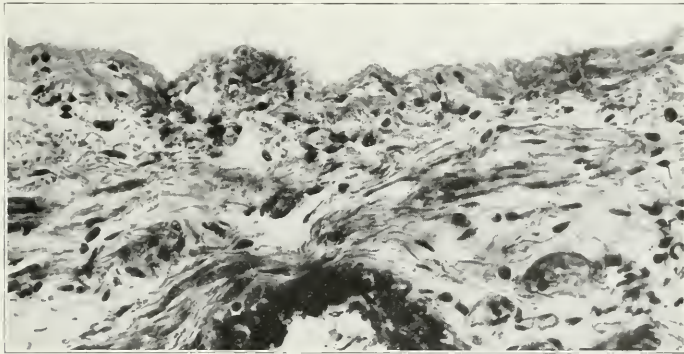


Fig. 3.—Case D. Medium sized bronchus showing edema of wall and loss of epithelium. $\times 250$.

On admission he complained chiefly of weakness, pain in the throat and chest, and intense dyspnea.

Examination.—Examination showed a well nourished man with slightly dilated heart, of rapid, feeble action, soft pulse. He was suffering at the time of the examination from very severe dyspnea, with extremely rapid, shallow respiration and marked cyanosis. Prostration was very extreme, but the patient's mind was clear. The pupils were equal and reacted. The lips and tongue were intensely cyanosed; the throat was congested. The lungs showed marked dullness at both bases posteriorly; bronchovesicular breathing, with slightly bronchial voice and scattered râles, most marked over the right base. The extremities were cold and cyanotic. The temperature ranged from 100 to 102 F.; the pulse from about 100 to 140; respirations from 44 to 60, during the patient's stay in the hospital. He was given oxygen inhalations, and blood was drawn for examination. It was very dark in color but when examined spectroscopically showed oxyhemoglobin only and no evidence of carbon monoxid² or methemoglobin. Under the stimula-

2. Illuminating gas poisoning had been suspected.

tion of the oxygen inhalations the patient got along fairly satisfactorily for several days. Examination of the urine showed: Specific gravity, 1.026; albumin, 2 per cent. by volume; a few leukocytes, mucus, and red cells; no casts. Repeated examinations gave the same findings, except that three days before death the urine contained a trace of albumin only and a few hyaline casts. The day before the patient died there was 5 per cent. of albumin by volume, with a few hyaline and granular casts.

During the last few days the patient's respiration was very labored; he was restless and complained of headache and nausea, and was able to sleep only a few hours during the night. The day before he died he became very restless and was irrational; the pulse was very feeble and irregular, and breathing was increasingly difficult. While there was at times an annoying cough, this was never a prominent symptom. The only alteration in the physical signs noted

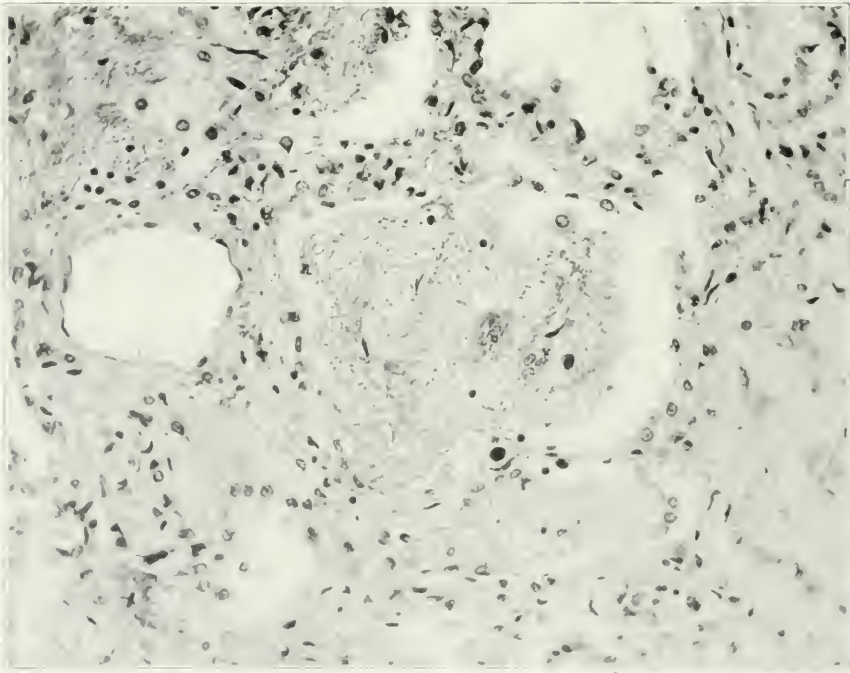


Fig. 1.—Case D. Fibrinous and hyaline exudate. $\times 250$.

was an increase in the area of dullness in the lungs and evidences of congestion and edema of the upper lobes.

The red blood-cell count was 5,100,000 with normal morphology; the hemoglobin was 90 per cent. The white blood-cell count was 17,000; polymorphs 68 per cent., lymphocytes, 30 per cent., basophils, 2 per cent.

Necropsy.—At autopsy, which was done after embalming with a fluid containing formaldehyd, the important gross lesions found were as follows:

1. An irregular cavity with sharply defined walls in the corpus striatum on each side of the brain, containing a clear, colorless fluid.
2. A moderately dense lobular pneumonia in the lower and posterior portion of the lungs on both sides.

The liver and kidneys showed nothing abnormal. The heart was dilated and looked pale and fatty.

Microscopical Examination.—The microscopical examination of the tissues was not at all interfered with by the previous embalming, the organs being in excellent condition and thoroughly hardened.

The lesion in the brain was of especial interest, inasmuch as the patient had had a severe accident about a year before his death. Yet the examination of the tissues involved did not permit of a connection between this lesion and the accident for the following reasons: First, the cavity contained clear watery fluid, which was not blood stained. Such a fluid would be seen only in either a congenital or a parasitic cyst of the brain, and such a lesion would not in all probability be symmetrical. Second, the walls of the cavity were perfectly sharp. Microscopical sections showed that the individual brain cells along the walls were perfectly preserved, and that small capillary vessels had been torn across, the ends still remaining open. There was not the slightest evidence of an inflammatory reaction or the formation of a membrane. It is probable, therefore, that this tear was formed post mortem by the injection at high pressure of the

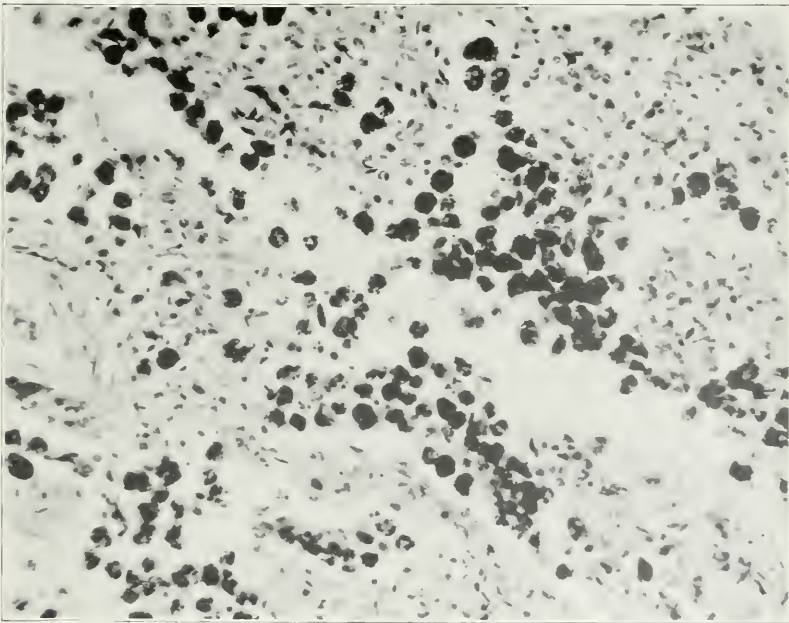


Fig. 5.—Case D. Areas containing chiefly pigmented cells. $\times 250$.

embalming fluid. That this is possible was proved by some experiments on human cadavers in which similar artefacts were induced. The vessels may have been weakened by the action of the poison, especially as Tomellini³ has shown that in acute nitrite poisoning small hemorrhages can be found in the organs, usually confined, however, to the stomach, intestine and liver. As stated above, small quantities of nitrous acid may be formed when nitrogen tetroxid comes in contact with moisture. Such nitrous acid would naturally combine with the free alkali in the tissues and blood and circulate as sodium nitrite. This might be the cause also of the very soft and rapid pulse occasionally seen in these cases of poisoning, and suggests an explanation for the very dark color of the blood noted in almost all cases of this form of intoxication, it being well known that nitrites

3. Tomellini: Beitr. z. path. Anat. (Ziegler's), 1905, xxxviii, 395.

form methemoglobin on contact with blood. The amount, however, is, as previously stated, usually too small to give a characteristic spectrum.

The liver and kidneys showed practically no changes on microscopical examination. A large number of sections from the liver showed a very few small necroses and a little fatty degeneration. The kidneys also were in good condition with only a slight cloudy swelling of the tubular epithelium and some congestion of the tufts in the capsules and of the intertubular vessels; but there were no casts in the tubules and no evidences of interstitial nephritis.

The heart muscle showed a small amount of fat infiltration, but was otherwise normal.

The interesting lesions were those in the lungs. As stated above, there was a lobular pneumonia chiefly in the lower lobes. Between the areas of consolidation there was a very marked emphysema with absorption of a large number

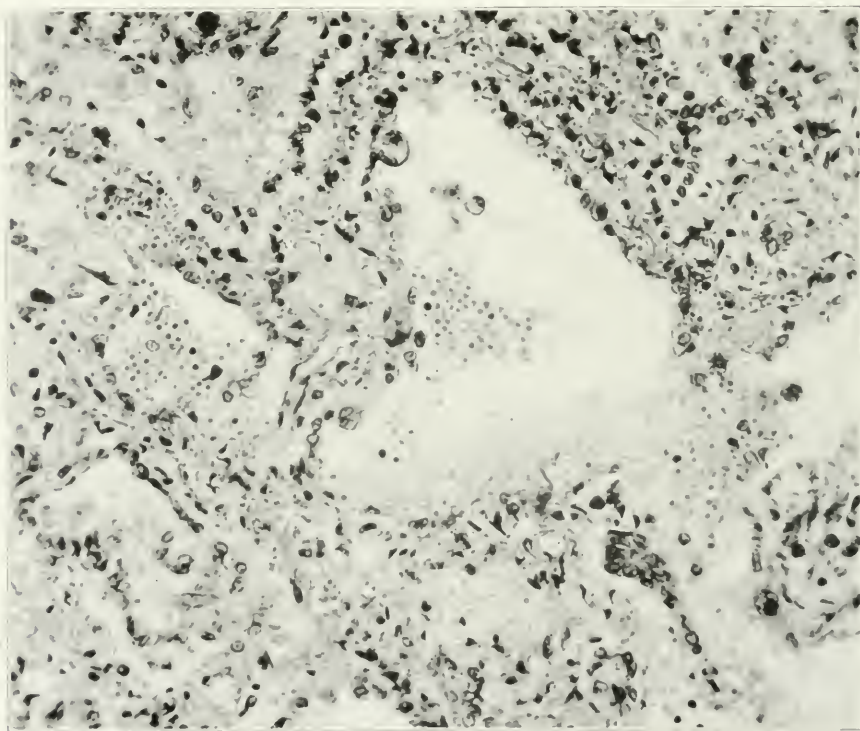


Fig. 6.—Case D. Hemorrhagic portion of lung. $\times 250$.

of alveoli so as to form large cavities easily visible to the naked eye, a phenomenon which regularly occurs not only in human beings, but also in experimental animals. (Figs. 1 and 2.) The mucous membrane of the trachea and bronchi was desquamated over extensive areas. (Fig. 3.) In some places fragments of the epithelial lining could be found still adhering to the walls or collected in masses in the lumen, with extreme edema of the subepithelial connective tissue. Occasionally a bronchus was found into which had grown a cellular plug largely filling the lumen. About the smaller bronchi were areas of consolidation, the alveoli being filled either with a transparent albuminous mass, or with fibrin containing a few leukocytes, or with desquamated alveolar epithelium. (Fig. 4.) In some places the epithelium was full of phagocytized blood pigment. (Fig. 5.)

Throughout, many alveoli contained red blood corpuscles. (Fig. 6.) The capillaries in the walls were distended with blood and the walls themselves were very edematous and much thickened. In places there was evidence of beginning regeneration of the alveolar epithelium which either lined the alveolus (Fig. 7) in the form of a thin flat layer of cells much more prominent than is seen in a normal lung, or occurred as swollen prominent hemispherical cells protruding into the lumen. Sometimes these cells formed considerable masses or were fused into syncytial bodies. (Fig. 8.) A true organizing pneumonia could hardly be said to be present. The fibrinous plugs occasionally became very dense and were covered with new epithelium, and in rare instances were penetrated by fibroblasts, but this was not at all a predominant lesion. In other portions of the lung the alveolar structure had entirely disappeared, the lung being quite collapsed and the regenerating epithelium showing as solid syncytial masses or as strands of cells lying in the fairly dense pulmonary tissue. (Fig. 9.) The upper portions of the lungs were fairly well aerated and showed a moderate emphysema, but no

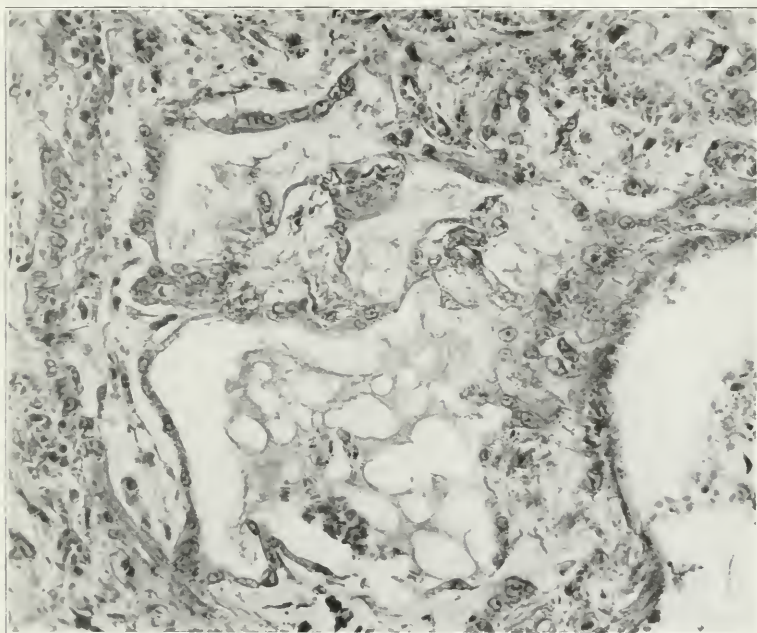


Fig. 7.—Case D. Regeneration of alveolar epithelium. $\times 250$.

other lesions. The bronchial lymph-nodes were edematous and heavily pigmented; but otherwise normal. In the smaller vessels of the lungs there were a number of parietal thrombi; occasionally a thrombus filled the entire vessel; and there was some proliferation of the endothelial lining, showing that these thrombi were undoubtedly ante mortem. Similar thromboses can be easily induced in animals by the inhalation of nitrogen tetroxid fumes. Obviously, no cultures could be made from the lung, but a large series of sections were stained by the various methods used for detecting bacteria, and no organisms could be found. The condition was evidently a non-progressive pneumonia due to irritation of the corrosive gases inhaled, and showing a tendency toward repair.

The history and clinical symptoms of the case and the nature of the lesions, which correspond exactly with those described in other cases of nitrogen tetroxid

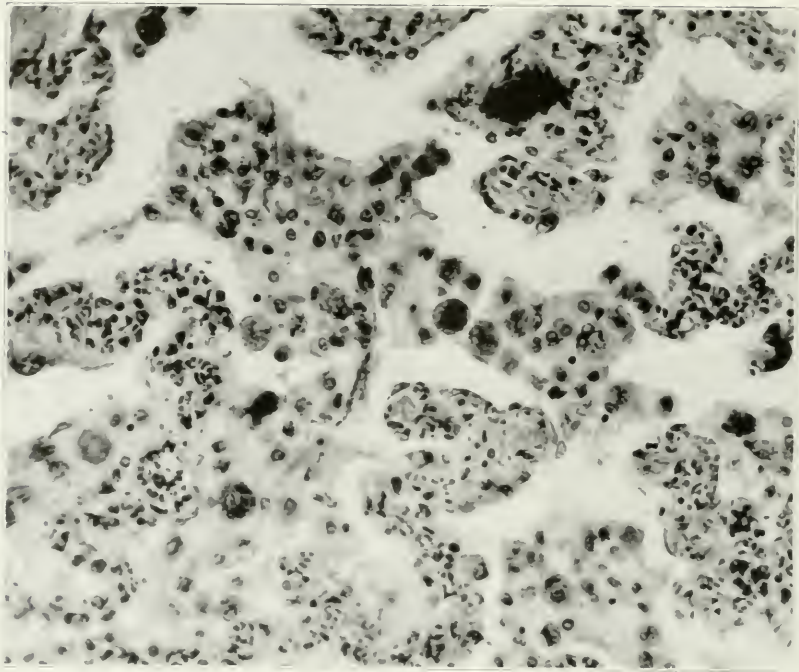


Fig. 8.—Case D. Cellular exudate, $\times 250$.

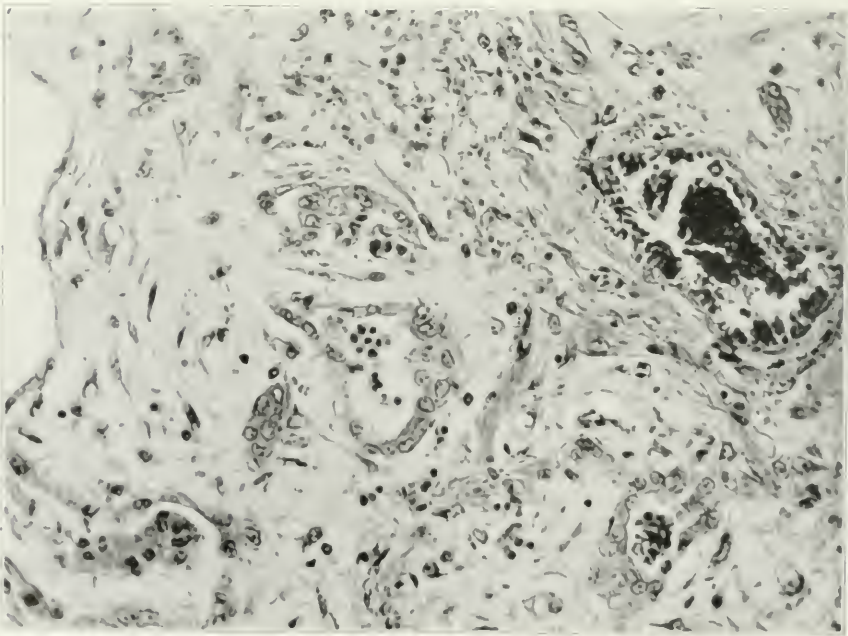


Fig. 9.—Case D. Collapsed and edematous lung with new growth of alveolar epithelium and connective tissues, $\times 250$.

poisoning, and the confirmatory results of animal experimentation which follow, point, it seems to me, to the conclusion that death in this case was unquestionably due to the accidental inhalation of this gas.

CASES FROM THE LITERATURE

An examination of the literature of nitrogen tetroxid poisoning shows only a moderate number of carefully studied cases. Most of the earlier ones were insufficiently examined, and in few are there any microscopical reports.

Schubert, in 1911, was able to collect 213 cases of poisoning by nitrogen tetroxid, of which fifty-five were fatal. With very few excep-

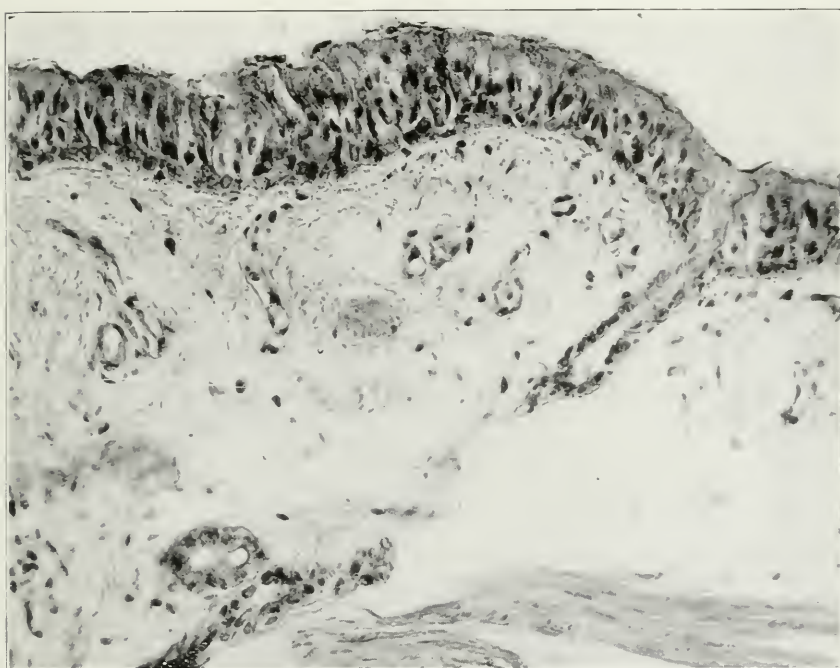


Fig. 10.—Dog 4. Bronchus showing epithelium and cilia still remaining, but marked edema and congestion of submucosa. $\times 300$.

tions, all these cases occurred in the last fifteen years, and chiefly in the German Empire. There are no doubt many cases which have never been published for obvious reasons. Concentrated nitric acid is extensively used in the manufacture of gun-cotton, nitroglycerin, smokeless powder and celluloid, and it is said that many cases of poisoning occur in these factories. The following reports include only those in which an autopsy was performed.

The most carefully studied cases are the four which were reported from Cologne following the breaking of some carboys of nitric acid in a

small room about 12x6x8 feet. The clinical histories were reported by Savels;⁴ the pathological findings by Loeschke,⁵ and the medicolegal aspects of the cases by Czaplewski⁶ and Schubert.⁷ While the reports do not wholly agree in minor details, the important findings are given so fully that a very satisfactory picture of poisoning of this type is presented. For this reason a full abstract of these cases is given here.

CASE 1.—B. K. The patient was a man, 42 years old. He was cleaning out the room after the accident and remained in it for about twenty minutes, when he felt weak and went home. He vomited and had diarrhea, and some hours after the accident was seized with intense dyspnea, cyanosis, and cardiac weakness. He died in the hospital about five and a half hours after he had

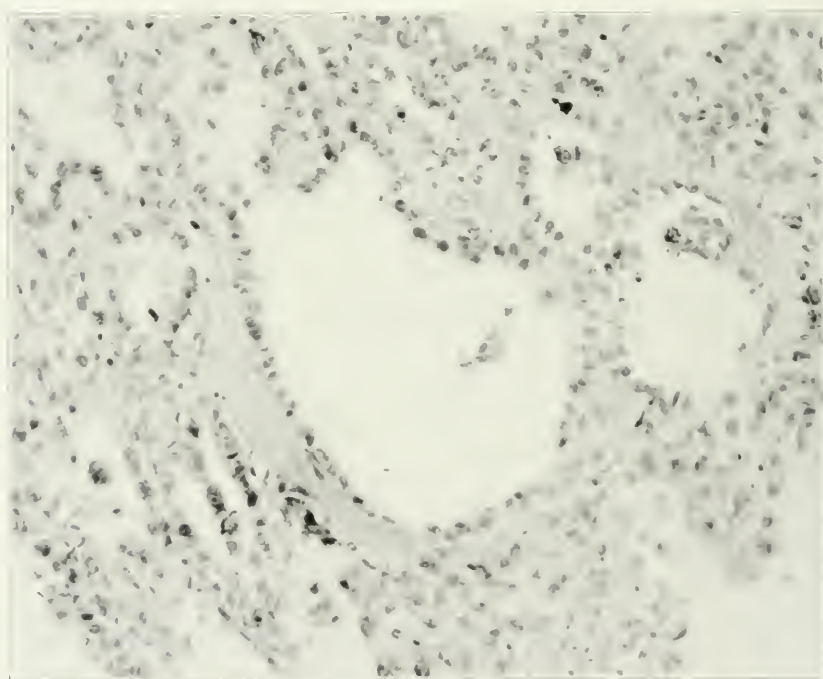


Fig. 11.—Dog 4. Terminal bronchus and alveoli with swollen and desquamated epithelium. $\times 300$.

left the room in which he was exposed to the vapor. The autopsy showed chiefly emphysema and edema of the lungs. Section of the lung had a violet red color and showed many bright red spots which were especially well aerated. A very abundant, foamy, pale-red fluid exuded from the cut surface. In the bronchi and trachea there was much thin, foamy secretion with small amounts of thick mucus. The mucous membrane was a bluish-red color. Microscopically the brain showed

4. Savels: *Deutsch. med. Wochenschr.*, 1910, xxxvi, 1754.

5. Loeschke: *Beitr. z. path. Anat.* (Ziegler's), 1910, xlix, 457.

6. Czaplewski: *Vrtljsch. f. gerichtl. Med.*, 1912, xliii, 356.

7. Schubert: *Ztschr. f. Med. Beamte*, 1911, xxix, 557.

no lesions except small perivascular hemorrhages. The kidneys showed intense congestion with some necrosis in the ascending branch of Henle's loop. The lungs showed marked emphysema with intense congestion; the alveolar epithelium was very largely desquamated and lay in masses in the alveoli. In the alveolar walls and also in the lumen there were numerous red cells and abundant leukocytes, and in some regions the walls of the alveoli were covered with a hyaline exudate. The mucous membrane of the bronchi was not altered microscopically. The liver showed nothing especially noteworthy.

CASE 2.—Sch. Th. The patient was 41 years old and had always previously been well. While cleaning out the cellar he noticed no discomfort except irritation in the chest and occasional tendency to cough. After the accident he had a mild headache, some coughing without sputum, and a feeling of weakness.

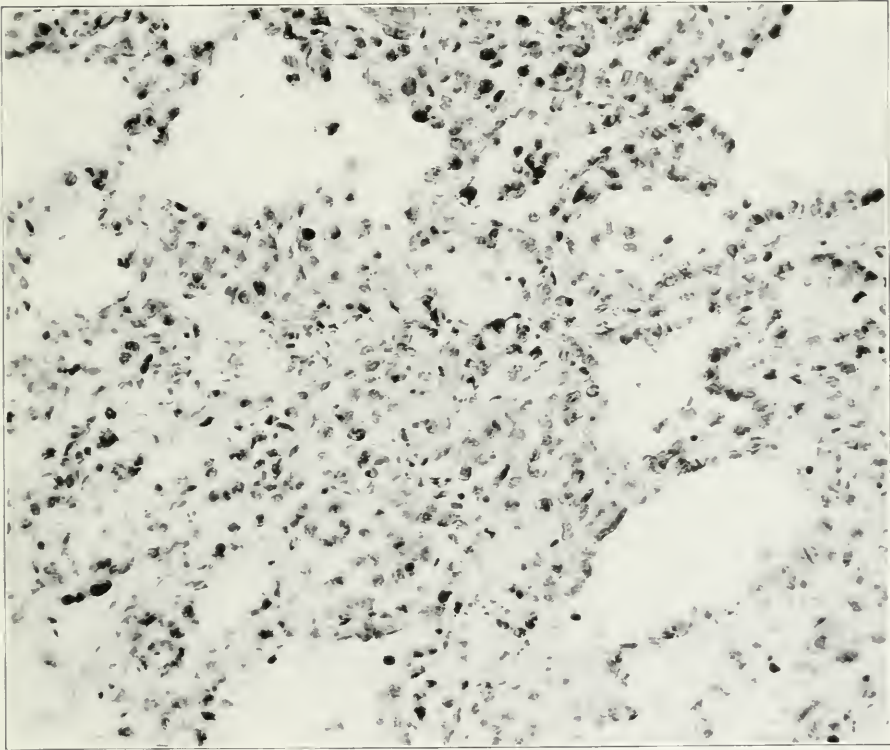


Fig. 12.—Dog 4. Desquamation of alveolar epithelium. $\times 300$.

Three hours after the accident he had pain in the chest and a chill, and went to bed, but could not remain there on account of extreme dyspnea, a feeling of pressure on the chest, and violent coughing. He was taken to the hospital, and on examination there was found to be extremely pale and cyanotic. The pupils were dilated, and reacted slowly to light; but otherwise there were no nervous symptoms. His mind was clear. Breathing was rapid and difficult with marked action of the auxiliary respiratory muscles. Over the lung there were sonorous percussion notes, with fine inspiratory crackles; no coughing; no sputum. The temperature was 101.1 F.; the pulse was rapid, 108, small and soft. The heart-sounds were pure. The patient had a venesection of 250 c.c. of blood,

which was strikingly dark and tar-like, and coagulated rapidly, but spectroscopically showed only bands of oxyhemoglobin. There was a slight increase in the number of white cells. In spite of oxygen inhalations the patient became rapidly worse; he complained of a feeling of compression of the larynx, of intense thirst, and of frightful dyspnea. The face was covered with sweat, the eyes protruded, and he could scarcely speak; the pulse became more rapid, rising to 140, and the temperature was 101.8 F. He died in coma forty-eight hours after the accident with signs of edema of the lungs, the final temperature being 102.9 F.

The urine passed during his stay in the hospital was small in amount, highly colored, faintly acid, free from albumin, and contained only 1 per cent. of sugar. The ammonia was somewhat increased; acetone positive; aceto-acetic tests negative.

Autopsy showed the lungs to be greatly distended, covering the pericardium; they were very heavy. The pleural surface was smooth. Sections showed a large

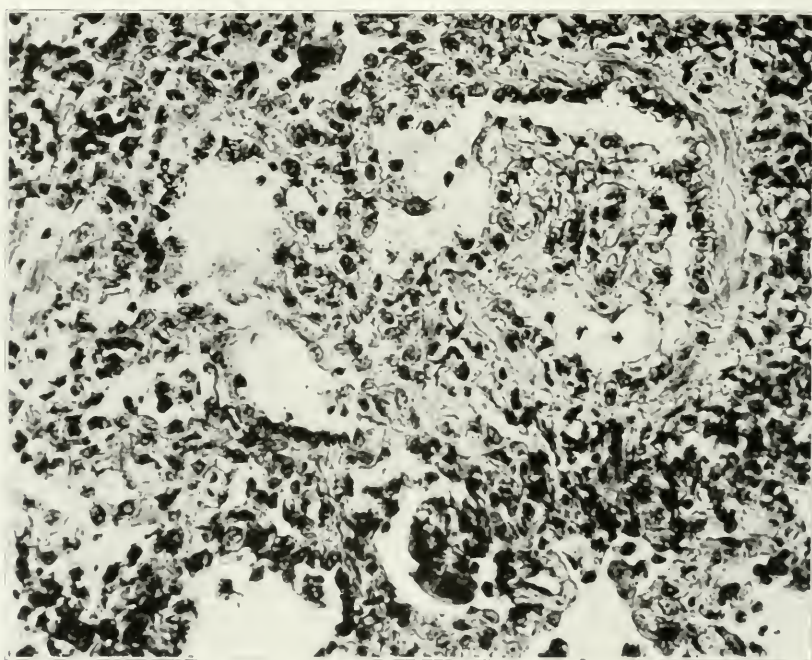


Fig. 13.—Dog 4. Intrabronchial growth of epithelium. $\times 300$.

amount of edema and congestion, with a general reddish color of the surface and numerous small granular areas scattered throughout, which were of a bright red color and emphysematous. The mucous membrane of the bronchi, trachea and pharynx was of a bluish-red color. The bronchial lymph-nodes were large and swollen. The brain was intensely congested; otherwise there was no change. The kidneys also were intensely congested, with no other change evident. The liver was pale and yellowish-brown and blackened on the application of ammonium sulphid.

Microscopically there were no changes in the brain. In the lungs the alveoli showed great variations in the dimensions. There were areas of relatively narrow alveolar spaces filled with exudate, partially fibrinous, partially hyaline, and containing many red and white cells. Between such areas there were large, greatly

dilated spaces, chiefly without content, apparently due to a traumatic emphysema, as shown by the spaces where the torn walls were hyaline and thrombosed vessels lay near the site of rupture. The epithelial coating of the alveoli was desquamated; that of the bronchi was present in areas though showing much degeneration; in other places it was entirely missing. All the vessels of the lung were greatly distended with blood. The spleen showed no special lesion except that there were many phagocytic cells containing blood pigment. The liver showed cloudy swelling with numerous areas of degeneration. At the periphery of these foci of necrosis there was already beginning repair with mitoses in the liver cells. In the kidneys the glomeruli tufts were very much distended, filling the entire capsule. In some parts of the capsule there was a small amount of hyaline exudate with desquamation of the capsular epithelium. The cells of Henle's loop were completely necrotic and in the convoluted tubules there was much yellowish

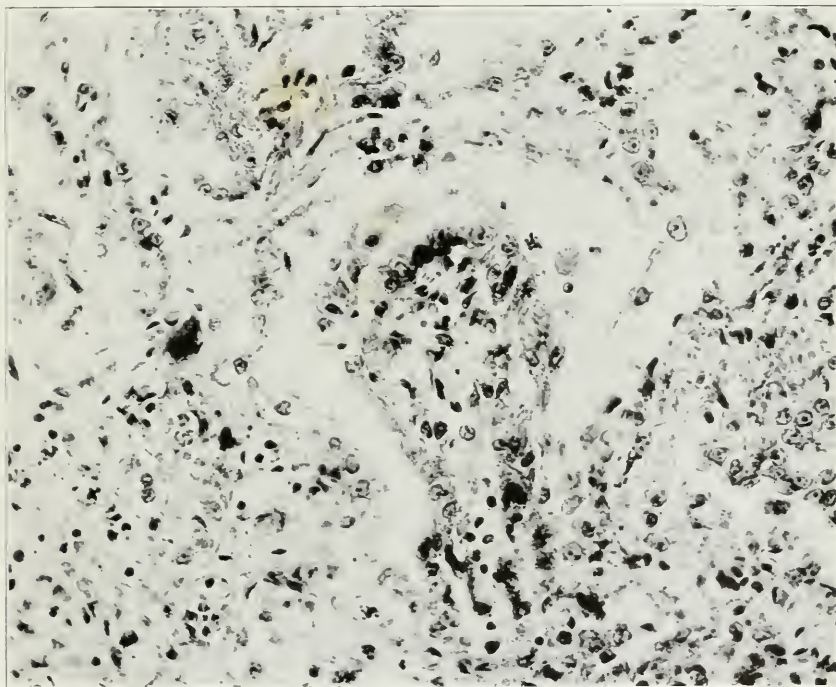


Fig. 14.—Dog 4. Intra-alveolar growth of epithelium. $\times 300$

granular pigment. Some of this pigment was contained in the tubular epithelium. Hyaline spherical granules were also found in the lumen of the tubules with an occasional hyaline cast.

CASE 3.—W. W. Previous to the accident the patient had always been well. On entrance to the hospital he complained of moderate pains in the chest, coughing and slight dyspnea. On examination he was apparently a healthy man in good condition. The skin of the face was reddish; the mucous membranes were slightly cyanotic. Breathing was a little rapid, percussion sonorous. All over the lungs there were sibilant râles, with a few moist râles over the lower right chest. The pulse was 108. There was some distention of the abdomen with diffuse tenderness. The stools were thin, and yellowish. During the day the

patient expectorated some yellowish sputum, and some faintly bronchial breathing appeared over the upper lobe of the right lung; and also in the left lower lobe there was moderate dulness with many respiratory râles. The temperature rose to 39 C. The blood obtained on venesection was dark and of a bluish color, but spectroscopically showed only oxyhemoglobin. There were no abnormalities in the urine. Two days after the accident the patient's mind was clear; he suffered from fever between 39 and 40 C. with irregular remissions. There was bronchial breathing over the right upper lobe and left lower lobe, and edema over the rest of the lung. The sputum was brownish-red, thin and foamy, and looked like pneumonic sputum, but no pneumococci could be found. Five days after the accident the patient had a moderate delirium. Venesection seemed to improve the general condition, but six days after the accident the heart action

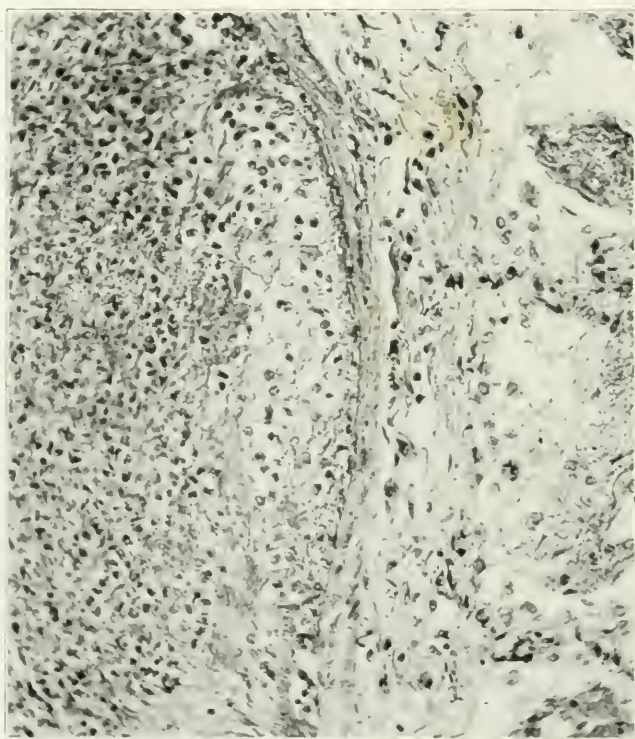


Fig. 15.—Dog 4. Thrombus in a vessel; blood clot to the left; lung tissue to the right. $\times 300$.

became very feeble, the pulse was irregular, and the condition progressively became worse; the dyspnea increased, with restlessness and picking at the bed clothes. The patient died seven days after the accident with evidences of pneumonia and cardiac failure. At no time did the urine show any important changes.

The diagnosis at autopsy was croupous pneumonia in the upper lobe on the right side and the lower lobe on the left; edema of the lungs; localized necrosis in the liver. The upper lobe of the right lung showed fresh adhesions. Both lungs were very large and heavy. On section the whole right upper lobe was granular, in a state of red hepatization, and absolutely free from air. There

were fibrinous plugs in the bronchi. The middle and lower lobes were edematous and contained some areas of pneumonia. The left upper lobe and the upper part of the lower lobe were extremely emphysematous. The lower part of the left lower lobe was largely granular, free from air, and in a state of red hepatization, with a few fibrinous plugs in the bronchi. The trachea and bronchi were filled with large amounts of foamy fluid. The liver was enlarged and intensely congested, and showed on cross section a grayish-red, cloudy appearance with some grayish areas scattered throughout. Both kidneys were very large, the capsules slightly adherent, the markings indistinct. The spleen showed intense congestion.

On microscopical examination of the lungs the alveoli in the pneumonic portion were partly of normal dimensions, partly very greatly dilated and filled with exudate which consisted chiefly of fibrin, but in places, of a smooth hyaline material. In this exudate there were found in varying numbers cells chiefly of polynuclear structure. In some regions the staining capacity of the alveolar wall was lost and in these areas the exudate seemed to have spread from one alveolus to another. The leukocytes were especially abundant here. Some of the blood-vessels were thrombosed, but the blood-supply of the consolidated areas was slight. The alveolar epithelium was absent over considerable areas. In some places there were isolated epithelial cells with long projections extending over the alveolar wall, evidently a beginning regeneration. The projections came into contact with the nearest epithelial cells, and in this way large areas of alveolar substance had been covered with a few flat cells. In areas where the regeneration had gone further the cells were thicker and more cubical, though at the periphery of these areas they still retained the flattened form. The cell boundaries were often so obscured as to suggest syncytial structure. Finally, some alveoli were entirely covered with cubical epithelium, occasionally much higher than the normal. No mitoses were observed. The epithelium of the smaller bronchi was still preserved. In the portions of the lung not involved in the pneumonia the alveoli were partly free from exudate and partly contained larger or smaller amounts of fibrin, leukocytes and red cells. The fibrin in places had undergone hyaline degeneration. The epithelial regeneration in these areas had progressed further than in the hepatized portions, so that most of the alveoli were covered with a thin, flat epithelial layer. No bacteria could be found.

Section of the liver showed areas of necrosis in the center of practically all of the acini. The central vein was frequently thrombosed. Polynuclear leukocytes were scattered through the necrotic tissue. The liver cells at the periphery of the acini were large, their nuclei rich in chromatin, and showed mitoses. Pigmentation of the liver cells was slight in amount.

The glomeruli of the kidney were large; the capsules were thin, with moderate desquamation of the capsular epithelium. In the capsules were found finely granular masses of albumin, in places compressing the glomerulus. The epithelium of the convoluted tubules was swollen, and many cells showed imperfect staining qualities. The lumen of the tubules contained granular masses of albumin. In Henle's loop there was extensive necrosis of cells, many of which had fallen off in the lumen. The collecting tubules showed numerous small homogeneous casts composed apparently of masses of tubular epithelium. They stained dark with hematoxylin and black with silver; in other words, they probably contained some phosphate of lime, a condition found chiefly in cases of poisoning with mercuric chlorid.

CASE 4.—A. S. This patient was not engaged in cleaning up the acid, which had been completed, but as night watchman had to pass through the cellar every hour. During the day following his night work he complained of pain in the chest and abdomen. When examined he was found to have symptoms of a severe bronchitis with very rapid and irregular heart. He complained also of dizziness and faintness and vomited a good deal. Twelve days after the accident he was seized suddenly with a cerebral hemorrhage and died three days later. Autopsy showed extensive arteriosclerosis with an area of red softening

about 2 cm. in diameter in the left posterior portion of the internal capsule. The hemorrhage was encapsulated but had broken through into the ventricle, which was filled with fluid blood. In this case the influence of the nitric oxid fumes was probably entirely secondary, as the lungs showed no lesions, but the coughing and vomiting may have induced the cerebral hemorrhage.

This completes the Cologne series. The following reports, while in the main less complete, are of sufficient importance to warrant their inclusion:

CASE 5.—This is an exceedingly interesting case reported under the title "bronchiolitis fibrosa obliterans."⁸ The patient survived the inhalation of the nitrogen tetroxid for nineteen days, so that the description shows well the nature of the lesions and the repair which takes place in a long continued case. From the microscopical findings given it is evident that the regeneration of the alveolar epithelium was nearly complete, though the cut shows some alveoli still filled with large cells; but in any case the desquamative lesions of the lungs were less striking than the organization and closure of the bronchi and small vessels with new-formed tissue.

The patient was a laborer, 25 years old, who was previously healthy; he inhaled the fumes from a vessel containing nitric and sulphuric acids with a piece of brass casting. (Such a combination gives nitrogen tetroxid vapors.) Immediately afterward he had a severe attack of coughing with a feeling of oppression on the chest and a good deal of pain in this region. During the course of the night following he was seized with intense dyspnea and entered the hospital. On admission it was noted that he was intensely cyanotic; temperature, 102; pulse, 112; respirations, 72; blood-pressure, 105 mm. There was slight dulness over both lungs posteriorly and coarse and fine crepitant râles all over. The patient complained of a feeling of burning behind the sternum. The sputum was small in quantity, reddish-brown and mucoid. The following day the temperature was normal and the cyanosis and dyspnea diminished. Respiration went down to 60, and the pulse to 108. The râles in the anterior portion of the chest diminished. Two days after the accident the patient coughed up rust-colored balls of sputum, showing very few diplococci. From the third to the seventh day after the accident the temperature rose slightly, and there was subcutaneous emphysema of the anterior thorax between the second and fifth ribs. Eight days after the accident the subcutaneous emphysema disappeared and the patient was in fairly good condition without symptoms, except a few râles in the chest, until four days later when the cyanosis and dyspnea returned. The respirations rose to 60 and the pulse to 120. The condition was not so serious as at the first attack. The râles returned with a change in the percussion note. The sputum was reddish-brown and mucoid. The patient died nineteen days after the accident.

At autopsy, the heart showed slight hypertrophy of the right side. The lungs were very much dilated, so that their borders touched each other at the level of the second and fourth ribs. A few fibrinous adhesions at the left apex and left lower lobe. On the surface of the lung there were a number of somewhat depressed bluish spots of irregular outline which contained less air than the rest of the tissue. On section, these were edematous. Scattered throughout the lung also were small areas of hepatization. In addition there were numerous small nodules of a transparent gray color looking a good deal like tubercles. The small vessels contained thrombi. The right lung also was voluminous and distended with air. In the middle lobe there was an area of hepatization about the size of a cherry. On the surface were numerous bluish-red spots, on the pleural surface of which were small fibrinous coagula. The cut surface showed

8. Fraenkel: Deutsch. Arch. f. klin. Med., 1902, lxxiii, 484.

many irregular dark-red areas, and besides these, small grayish-white nodules attached to the smaller bronchi. There was an emphysema of the lung with numerous areas 2 to 3 mm. in diameter. The smaller arteries showed thrombi adherent to the walls. The other organs showed nothing but congestion.

Microscopical examination of the lung showed a large number of thrombosed small arteries and the hemorrhagic and edematous areas which Fraenkel was inclined to interpret as small infarcts. In the fine terminal bronchi there was a marked epithelial desquamation, the cells often filling the entire lumen. The larger bronchi also showed considerable loss of epithelium. In the finer branches of the terminal bronchi there was a growth of connective tissue reducing the lumen in many cases to a small slit, covered in part with high cylindrical epithelium of the bronchial type. The remainder of the lung showed either emphysema, edema or collapse. In the denser portions the alveolar walls were thickened with connective tissue, especially near the bronchioles. Some of the vascular thrombi had undergone complete organization with the formation of connective tissue. There was no report of any bacteriological examination of the lung tissues.

In a later paper Fraenkel⁹ reports three more cases of so-called bronchiolitis obliterans fibrosa acuta, one in a plasterer who inhaled a large amount of lime and other dust, and the second in a man working in a drug store. The history of this latter case was very imperfect and Fraenkel says that it was not possible to exclude the inhalation of some irritating substance as the cause of the disease. In the third case reported no history was obtainable, and the diagnosis was made solely on the clinical symptoms of intense dyspnea, cyanosis and emphysema. Death occurred on the fourteenth day. Microscopical examination of the tissues showed chiefly obliteration of the bronchi.

The report is not very clear, but apparently all these patients lived for at least two weeks. The writer also observed another case with similar symptoms due to the inhalation of large quantities of dust from chlorid of lime. He says, however, that the disease is not always due to the inhalation of irritating gases or powders, and that measles and whooping-cough occasionally produce in children a very similar anatomical picture. In ordinary lobar pneumonia such a closure of the bronchi by the ingrowth of connective tissue does not occur or is very limited in extent, even in cases in which resolution is prolonged over weeks.

CASE 6.—The patient,¹⁰ 23 years old, a tinner by trade, inhaled the fumes from a mixture of hydrochloric and nitric acids. He had a slight oppression in the chest but continued at work for nine days though not feeling well. On the tenth day he had a good deal of dyspnea and entered the hospital. When examined he showed very marked cyanosis, especially of the face. Thoracic movements were limited during respiration, which was rapid and shallow. The pulse was 140, very soft and irregular. Temperature was 102.2 F. There was dullness over the chest. The patient appeared moribund. The sputum was abundant, yellowish and lumpy. There were physical signs of emphysema with many moist râles over the lungs. The next day respiration went to 50, the temperature was about 100.4 F.; the cyanosis and dyspnea increased, and the patient died twenty-six days after the exposure to the fumes. At autopsy the lungs did not collapse on opening the thorax. There were small hemorrhages in the pleural surfaces of the lower lobes. On section the lungs were densely sprinkled with small grayish nodules 1 to 2 mm. in diameter, which surrounded the smaller

9. Fraenkel: Berl. klin. Wehnschr., 1909, xlv, 6.

10. Edens: Deutsch. Arch. f. klin. Med., 1906, lxxx, 598.

bronchi. The mucous membrane of the larynx, trachea and smaller bronchi was intensely irritated, and in many places had disappeared. No other lesions were found in the body.

Microscopic examination showed marked inflammatory lesions of the trachea and bronchi with congestion and edema. In the lung there were numerous small chronic pneumonic areas with the formation of granulation tissue. The alveoli at the periphery of the pneumonic areas contained a cellular exudate chiefly composed of desquamated alveolar epithelium, the cells being of large size and often loaded with pigment. Some of the alveoli also contain fibrin. There was marked inflammation of the septa of the alveoli with edema, fibrinous exudate and leukocytes; the vessels were greatly distended. Thrombi were not noticed, and bacteria were not found in the lung sections.

This case is particularly interesting because of the long continuance of the disease, showing the latter stages of the process, death usually occurring much earlier in the course of the intoxication.

CASE 7.—Paul¹¹ reports the case of a laborer, 32 years of age, who was ordered to clean the deposit out of a lead chamber. This deposit consisted chiefly of lead sulphate mixed with some sulphuric acid, the mixture giving off vapors of some of the nitric oxids. For this reason it was necessary that the workers leave the chamber every few minutes as the stirring up of the mud set free the fumes. The chamber had been cleaned some two hundred times under exactly the same conditions as on the occasion of the accident. There were two other workers also in the chamber who were not in the least affected. The patient entered the chamber three times, remaining for periods of ten to twelve minutes. About 6 o'clock he went home without complaining in the slightest. Some hours afterward, however, he was seized with dyspnea and very severe coughing. He attempted to go to work the next morning, but collapsed on reaching the factory. The patient was examined by a physician after his collapse at the factory and was found to be intensely dyspneic with paroxysms of coughing. The sputum was brownish-red in color, having previously been bright yellow. The lungs showed some dulness over the lower lobes, but no bronchial breathing, only fine râles all over. The pulse was 110, very soft and small. Temperature was subnormal. About thirty hours after the exposure he had a severe seizure with extreme cyanosis, great restlessness and occasional delirium. He went into coma and died about forty-six hours after exposure to the gases with the symptoms of pulmonary edema.

Autopsy showed intense congestion of the membranes and substance of the brain with numerous punctate hemorrhages in the substance. The mucous membrane of the pharynx, trachea and larynx was very dark red and covered with sticky mucus. The heart's blood was very dark; the organ was dilated and the muscle was soft. The pleura of the right lung showed a number of small ecchymotic areas about 1 cm. in diameter. On section a large amount of reddish, foamy fluid escaped from the lung which was extremely edematous, with the peripheral portions showing a considerable amount of emphysema. Section of the left lung showed the same, but the pleura was adherent all over the thorax with old adhesions. The stomach showed a small hemorrhagic erosion at the greater curvature. There was no lesion except intense congestion of the viscera. No microscopical examination was reported.

CASE 8.—Schmieden¹² reported the case of a 24-year-old laborer who was exposed to nitrogen tetroxid fumes for one hour following the breaking of a carboy of nitric acid and attempts to stop the action of the acid by the use of sawdust. He noticed only slight dyspnea after finishing the work and on his return home

11. Paul: *Wien. klin. Wchnschr.*, 1895, viii, 665.

12. Schmieden: *Centralbl. f. klin. Med.*, 1892, xiii, 209.

some cyanosis. During the night the patient was unable to sleep on account of increasing dyspnea and very severe cough. On admission to the hospital he was found to be intensely cyanotic; respirations, 78; breathing chiefly abdominal with marked movements of the *alae nasi* and the sternocleidomastoid and scalenus muscles. Percussion note was tympanitic. Fine râles were heard all over the chest. The sputum was abundant, thin, rusty-brown in color like pneumonic sputum after edema of the lungs supervenes. The pulse was 112 and soft. Blood taken from the ear was brownish-black in color and on dilution in water became bright red; spectroscopically there was nothing abnormal. The patient died in coma thirty hours after the inhalation of the acid fumes with symptoms of edema of the lungs.

At autopsy the lungs were extraordinarily congested and infiltrated throughout with bloody edematous fluid. The mucous membrane of the bronchi was congested. The vessels of the lungs were distended with dark red and black thrombi. There was intense congestion of the pial veins and the arteries at the base of the brain. There was a yellowish slough on the mucous membrane of the stomach near the cardia. No microscopical examination was made.

CASE 9.—Kockel¹³ reported the case of an apparently healthy male, 65 years old, who had worked for about one hour in a room in which a large quantity of nitric acid had been spilled. Except for a little coughing and dryness in the throat there were no symptoms until six hours after exposure, when he was seized with very severe dyspnea, coughing, and a feeling of great anxiety. The symptoms increased rapidly with intense cyanosis, and the patient died two hours later. At the autopsy there was congestion of the meninges; in the posterior portion of the external rim of the right lenticular nucleus there was an area of softening the size of a hazel nut, apparently an old lesion. The heart muscle was soft; the cavities were much dilated and filled with dark fluid blood. The left lung was very voluminous; the tissues were soft and tore easily, and on cut section were very dark grayish-red. There was a good deal of edema and very little air in the alveoli. The right lung also was very voluminous; the upper lobe dark grayish-red and very much congested with only a moderate amount of fluid in the alveoli. The mucous membrane of the larynx, trachea and bronchi was bright red and much swollen. No microscopical examination was reported.

In addition to these reports of fatal cases with complete autopsies, there are a considerable number of reports of fatal cases with partial autopsies, and also of cases of mild types of poisoning, some of which are of sufficient interest to reproduce here.

Orfila¹⁴ collected two cases. In the first case, observed by Desgranges¹⁵ the fumes were evolved by the breaking of a flask of nitric acid, exposure lasting for about five minutes. The patient then went into the open air and recovered from the sensation of choking. He was very thirsty about four hours later, and twelve hours after exposure was seized with coughing and prostration, and seventeen hours after the accident had an attack of intense dyspnea with cyanosis, pain in the abdomen, convulsive movements, and delirium, and died about twenty-seven hours after the inhalation of the gas. There was no autopsy.

In the second case,¹⁶ a healthy man of 22 years inhaled a large amount of fumes set free on the breaking of a flask of nitric acid. Some hours afterward he took a walk in order to relieve a sensation of oppression in the chest. About nine hours after the accident intense dyspnea supervened. Forty-eight hours

13. Kockel: *Vrtljschr. f. gerichtl. Med.*, 1898, xv, 1.

14. Orfila: *Toxicologie*, Trans. by Kühn, Leipsic 1839, i, 124.

15. Desgranges: *Jour. de méd.*, continué, 1804, viii, 487.

16. Cherrier: *Eull. Soc. méd. émul.*, 1823.

after the gas was inhaled the patient died with typical symptoms. At autopsy the right lung was found to fill the entire half of the thorax; it was solid and edematous, most of the fluid appearing to be dark fluid blood. In the left lung there were large amounts of bloody fluid but some of the parenchyma was still well aerated. The mucous membrane of the trachea and bronchi was of a blood-red color. There were superficial ulcerations in the cardia and pylorus. The contents of the stomach were sour. The other organs showed no changes.

In a third case,¹⁷ a powerful man, 34 years old, was cleaning copper with nitric acid. After two days, during which time he had inhaled a considerable amount of the fumes of the acid, he was seized with headache, cough and oppression in the chest. Twenty-four hours later on examination he was found to have intense dyspnea, protruding eyes, purple lips, and frequent cough, with sticky, yellow sputum. There were coarse râles over the chest. He died twenty-four hours after the onset of the symptoms. At autopsy the lungs were very voluminous, crepitant and of normal color. The mucous membrane of the trachea and bronchi was vivid red and much swollen. The bronchi contained much yellow fluid and a similar fluid could be expressed from the lung tissue on section.

Manouvriez¹⁸ reported several cases, the exposure occurring when a warehouse containing sodium nitrate and other substances caught fire. One of the workmen made several attempts to remove the sacks and was exposed for a few minutes each time to the vapors of nitrogen tetroxid. After the third attempt he collapsed and was taken to his home. He complained of thirst and intense dyspnea with intense pain in the chest, and died about four hours after the exposure. His assistant died with the same symptoms about eight hours after the exposure. Another exposed person suffered from violent vomiting and diarrhea, but was ill for only two days.

Autopsies on the first two cases showed that the blood was black and acid to litmus paper, the latter seeming a rather remarkable condition in the light of our present knowledge of the great acid-neutralizing capacity of the blood and the fact that a change in reaction was not noted in any of the animal experiments which follow. There was intense congestion of the bronchi and lungs which were distended with blood and contained several areas of hemorrhage. Hyperemia of the mucous membrane of the stomach was noted, with congestion of the other organs.

Künne¹⁹ reported briefly eleven cases of intoxication due to the inhalation for only two or three minutes of fumes arising during a fire in a building in which a large number of carboys of nitric acid were stored. In some of the cases no symptoms appeared until six or eight hours afterward; the patients having stood about watching the fire, smoking their pipes, etc., and finally going home to bed and to sleep. They were awakened by intense dyspnea. Some of the patients vomited, and showed great cyanosis, nervous symptoms, and rapid and fatal heart action. There were two fatal cases, but these were not observed by Künne. Seven of the patients ran a mild course and were discharged nine days after the exposure as cured. Four others were much more seriously affected and were not able to return to work for two weeks after the exposure. The only exceptional point was that three of the patients showed albumin in the urine. All the others had the usual symptoms previously described.

Pearse²⁰ reported the case of a man, 25 years of age, who inhaled the fumes of nitrogen tetroxid on the breaking of a carboy of nitric acid. Six hours after the inhalation the patient had pains in the chest and difficulty in swallowing and talking. Eight and a half hours after inhaling the fumes he had an attack of

17. Suequet: Details are given by Chevallier and de Loury, *Ann. d'hyg.*, 1847, xxxviii, 323.

18. Manouvriez: *Bull. de l'Acad. de méd., Paris*, 1897, xxxvii, series 3, p. 306.

19. Künne: *Deutsch. med. Wochenschr.*, 1897, xxiii, 414.

20. Pearse: *Albany Med. Ann.*, 1899, xx, 28.

severe dyspnea; respirations, 40; high pitched respiratory murmurs over bronchi and right lung. The left lung was not involved. Bloody mucus was expectorated. Twenty-four hours after the accident signs of consolidation developed in the right lung with edema and cyanosis of the lips. The patient became delirious and died twenty-nine hours after inhaling the fumes, of edema of the lungs.

Wood and Stephen²¹ reported the case of a chemist who broke a bottle containing about three liters of nitric acid, and spent about half an hour in cleaning up the fluid by means of sawdust and cloth; he was not inconvenienced by the fumes. Eight and a half hours after the accident he began to suffer from intense dyspnea and expectorated large quantities of straw-colored fluid, nearly a liter in amount. Respirations, 62; marked cyanosis and very violent cough on the first day; cough less on the second day; none after the third day. Recovery was slow, the patient remaining in bed for ten days.

Harrington²² reported nine cases of poisoning by nitrogen tetroxid fumes following the breaking of a carboy containing nitric acid. None of the patients felt any bad effects until five to eight hours after the exposure, when they developed dyspnea, rapid respiration, cough, and in some cases delirium. There were no fatalities.

Lange²³ reported two cases of an organizing bronchitis which do not correspond either in the clinical history or in the general autopsy findings with the type of disease due to inhalation of irritating gases and are here quoted merely because they are frequently referred to in the literature of the subject. In the first case there was a history of cough for eight days, chills and headache, the patient entering a hospital and dying on the ninth day of the disease with a pneumonia, showing subpleural hemorrhages and numerous gray miliary nodules throughout the lung tissue, which proved to be fine terminal bronchi. Each small nodule was surrounded by about 1 mm. of dark colored lung tissue. The alveoli lying between these nodules showed no exudation. In the second case, the patient, 32 years old, had been sick for six months with cough and dyspnea. For four weeks before death he had great discomfort so that he was not able to work. Autopsy showed voluminous lungs, hemorrhagic spots in the pleura, and on the cut surface large numbers of small nodules which looked like miliary tubercles. These grayish nodules were surrounded by a narrow ring of reddish tissue. The lung between these areas was quite normal. The vessels showed no thrombi.

Pott²⁴ reported an instance in which nitrogen tetroxid fumes were formed by the action of acid phosphate on sodium nitrate, the mixture being a preparation used as a fertilizer. About thirty persons were exposed to the vapors, of whom two died, one in twelve hours and one in forty hours. There was no autopsy in either case. The symptoms were typical as described above. Eight persons were confined to bed for a number of days with very severe dyspnea and cough, the sputum being thick and yellow and containing blood and alveolar epithelium. In the most serious case the patient was confined to bed for eight days, but recovery was complete.

Hall and Cooper²⁵ reported a case in which a carboy of nitric acid was accidentally broken and the acid spread over the floor, attacking some zinc plates and sawdust and starting a fire. Twenty people were seriously affected, four of whom died, two on the second day and two several weeks later. Dyspnea was present in 100 per cent. of the cases, cough in 93 per cent., vomiting in 53 per cent. Cough with bloody expectoration persisted in 27 per cent. The patients who recovered were found to be more susceptible to cold than before. Two cases were autopsied. The records are very incomplete; it is stated that in one the lungs were large and voluminous and the bronchi filled with bloody

21. Wood and Stephen: *Australasian Med. Gaz.*, 1909, xxviii, 25.

22. Harrington: *Wisconsin Med. Jour.*, 1903, i, 177.

23. Lange: *Deutsch. Arch. f. klin. Med.*, 1901, lxx, 342.

24. Pott: *Deutsch. med. Wehnschr.*, 1884, x, 451.

25. Hall and Cooper: *Jour. Am. Med. Assn.*, 1905, xlv, 396.

fluid. There was much edema of the lung tissue and a thickening of the bronchial mucosa. The second case in which death occurred one month after exposure showed bronchopneumonia with consolidation of the lung, and microscopically the alveoli were filled with cells and beginning fibrosis.

Bauer²⁶ reported a case of an anilin factory worker who inhaled nitrogen tetroxid. After a short time he had dyspnea and cough, and he died in two days with pulmonary edema. An autopsy showed acute bronchitis, lobular pneumonia and edema, with thrombi in the pulmonary vessels.

ANIMAL EXPERIMENTS

In order to study further the lesions seen in the reported case, a series of experiments were carried out on dogs.

Among those who had made previous studies of acid poisoning on animals may be mentioned Lesser,²⁷ who exposed rabbits and dogs to the vapors given off on warming nitric acid. He showed that only occasionally bronchitis, bronchopneumonia, or edema of the lungs supervened. Even after exposing dogs for weeks to acid vapors he was not able to find any microscopical changes in the lungs. The reason for this is that the acid volatilizes unchanged and condenses in the nasal passages, and while it may corrode the tissues there does not penetrate further. Practically no nitrogen tetroxid is given off from ordinary nitric acid on warming.

Kockel, Bauer,²⁸ Gréhan and Quinquaud,²⁸ and Eulenberg²⁹ carried out animal experiments with nitrogen tetroxid. Those of Gréhan and Quinquaud and Eulenberg are not important here because the animals either died within a few minutes or recovered from the inhalation, and no microscopical examinations were made.

Kockel's animal experiments gave the following results:¹³ The blood of the animals dying in an atmosphere of nitrogen tetroxid fumes had a chocolate-brown color, but when the animals had a chance to breathe fresh air for a few minutes after inhalation of the gas, the blood was merely dark in color and not otherwise abnormal. The lungs were usually markedly emphysematous; the color was almost always bright red; and on section there were usually reddish areas and much edema. Extensive hepatisation was noted only in the animals killed four or five days after the exposure to the fumes. The mucous membrane of the respiratory passages was congested and edematous. The spleen and kidneys showed no gross lesions. The liver was occasionally intensely congested. In some animals swelling, edema and ulceration of the mucous membrane of the stomach and intestine was observed. Microscopically, the chief lesion in the lungs was intense hyperemia with

26. Bauer: Original report not accessible. Few details given. Abstract in *Virchow-Hirsch, Jahresb.*, 1895, p. 460.

27. Lesser: *Ztschr. f. physiol. Chem.*, 1877, i, 165.

28. Gréhan and Quinquaud: *Compt. rend. Soc. de biol.*, 1884, viii, t.i, 469.

29. Eulenberg: *Vrtljschr. f. gerichtl. Med.*, 1876, xxv, 209.

hyaline thrombi in the capillaries, a condition also observed by Bauer. Thrombi also were found in the larger vessels leading to the lungs in some cases. An extensive edema of the lung tissue involving the perivascular and peribronchial connective tissue and also the alveolar walls was quite common. Over areas of moderate extent in the lungs the alveoli contained serous or fibrinous exudate. In the animals which survived for a number of days there was almost always a bronchopneumonia, the alveoli being filled with red and white cells and desquamated epithelium. Four or five days after the inhalation a considerable pneumonic infiltration was usually present, the alveoli being filled with desquamated epithelium, which not infrequently fused to syncytial-like masses. The parts of the lungs free from edema and exudate were emphysematous. Plugs of epithelium and leukocytes cemented with mucus often filled the smaller bronchi. Multiple focal necroses were occasionally present in the liver.

Spectroscopical examination of the blood showed that the chocolate-brown color observed in the animals dying in an atmosphere of nitrogen tetroxid fumes was due to the formation of hematin. This substance was also observed by Kobert in the urine of a patient, but is not as a rule demonstrable in those patients who have survived exposure to the gases. Probably only very small amounts of this substance are formed in the blood. No morphological changes in the circulating blood were noted.

The necroses occasionally observed in the mucous membrane of the stomach and intestine were undoubtedly due to the fact that some of the fumes had dissolved in the saliva and been swallowed, causing erosions. The results of the animal experiments, therefore, correspond quite closely with the lesions found in human beings.

My own experiments confirm and extend Kockel's results. A few characteristic protocols are appended. Dogs were selected for the experiments because of the ease with which pneumonia is induced in these animals and because the lungs are voluminous enough to permit of considerable topographical variation in the pneumonic areas.

DOG 1.—Large, powerful animal weighing about 15 kilos; was anesthetized with ether and allowed to fill his lungs four times with fumes of nitrogen tetroxid mixed with about an equal volume of air. The animal revived from the ether and seemed pretty well for some hours, but on the following morning was suffering from severe dyspnea both inspiratory and expiratory. He remained quietly in his cage and refused to eat. He coughed a good deal, and forty-eight hours later was killed. The lungs showed an acute bronchitis with edema, desquamation of the bronchial epithelium, and a small amount of lobular pneumonia, the alveoli containing large cells, many of them pigmented, and a good deal of fibrin and a few leukocytes. The remainder of the lung was deeply congested and showed a good deal of edema with a marked emphysema especially in the anterior portions. The other organs showed no lesions. Cultures from the lungs were sterile. The condition corresponds to that noted in persons dying soon after inhaling the gas.

Dog 3.—Terrier, weighing about 10 kilos, was lightly chloroformed and allowed to fill his lungs about twelve times with a mixture of equal volumes of air and nitrogen tetroxid. The animal died about ten minutes later and on removal the lungs were found to be almost solid with edematous bloody fluid. Microscopically the alveoli were filled with a serous edema containing many red cells. No lesions were present in the other organs. A similar condition has been noted in some of the rapidly fatal human cases.

Dog 4.—Terrier, weighing about 9 kilos, was lightly chloroformed and allowed to fill his lungs three times with a dilute mixture of air and nitrogen tetroxid. It soon recovered but refused to eat, had a good deal of difficulty in breathing, with coarse râles over the chest, and coughed a good deal, raising yellowish frothy mucoid sputum. The animal was killed after five days. The lungs showed extreme emphysema with a scattered lobular pneumonia (Fig. 2) most marked in dependent portions. The bronchi were congested and filled with mucus. There were no other macroscopic lesions. Microscopically the lungs showed extensive lesions; the other organs were normal except for a few focal necroses in the liver. The bronchial mucosa was extremely edematous and congested, but the epithelium was still intact (Fig. 10), the cilia even being present in a few areas. The epithelium of the terminal bronchi was swollen and desquamated (Fig. 11), as was that of the alveoli (Fig. 12). The alveolar walls were thickened and edematous, and the capillaries congested. Emphysematous areas alternated with patches of pneumonia (Fig. 2). There were plugs of epithelium in the terminal bronchi (Fig. 13), some of them composed wholly of cells, others of cells covering a growth of fibrous tissue. This is the lesion described by Fraenkel as "bronchiolitis fibrosa obliterans." Similar plugs filled some of the alveoli (Fig. 14), others contained solid masses of desquamated cells, others were filled with blood, fibrin and coagulated serum; still others were lined with unregenerating epithelium. Mitotic figures were rare, though present. A number of the smaller vessels showed thrombi in various stages of organization (Fig. 15.). The lesions in the lungs were very irregularly distributed and corresponded very closely in all details with those of the case of D, here reported, except perhaps in the extent of the emphysema, this lesion being less marked in the dog than in the human material, while the bronchiectasis was more extensive in the animal.

Dog 5.—Irish terrier, weighing 7 kilos, was etherized and given ten breaths of very dilute nitrogen tetroxid. Nineteen days later the dog still had a cough but otherwise seemed well. It was then given four deep breaths of dilute nitrogen tetroxid, and eighteen days later three inhalations of the same. Six weeks later it was killed. The lungs seemed normal in the gross, and microscopically it could not be determined that there were any changes; possibly the lungs were slightly more emphysematous than those of a normal dog, but repair was extraordinarily complete.

Dog 6.—Fox terrier, weighing about 9.5 kilos, was given, under ether anesthesia, six breaths of dilute nitrogen tetroxid and air mixture. The following day the dog was very quiet, did not seem to suffer very much pain, but coughed a good deal and showed intense dyspnea. The second day after he coughed up thin, foamy sputum, did not eat, and vomited small quantities of mucus; for six days he coughed continuously and was then killed. On opening the thorax the lungs were found to be covered with a thin layer of fresh fibrin which was especially abundant over patchy areas of deep congestion. These congested areas were scattered irregularly throughout, and were especially abundant near the thin edges of the lobes; they were quite firm to pressure. The remainder of the lung was well aerated. The bronchi were filled with thick mucus; the mucous membrane was congested. The bronchial lymph-nodes were not enlarged. The kidneys and other organs appeared normal. The brain showed no hemorrhages nor softening. Microscopically the lungs showed irregular areas of lobular pneumonia with fibrin, a few leukocytes, and many desquamated alveolar epithelial cells. There was considerable fusion of the alveoli to form large open spaces.

The alveolar walls were much thickened and congested. There was beginning repair of the epithelium in some of the alveoli. The kidneys and liver showed no microscopical changes. Cultures from the lung were sterile.

Dog 7.—Short-haired, female terrier, weighing 9.4 kilos, while under morphin was given three deep breaths of the concentrated gas. The animal was very dyspneic for a few minutes and then became active and apparently suffered no discomfort. Six days afterward it was coughing a good deal. One month later it was apparently entirely well and healthy, and was then put under the influence of morphin and given two exposures to nitrogen tetroxid fumes, about two hours apart. The day following the animal appeared very sick and refused to eat or drink. Râles in throat and difficult breathing. Two days later it was still coughing up a white mucous sputum. The animal was very quiet and refused to eat. Five days later it was killed. The lungs were very voluminous. There were firm sunken areas along the borders of the posterior portions of the lobes. These areas were of a grayish color. The bronchi protruded from the surface of the cut lung and contained a mucopurulent fluid. The solid lung tissue was greenish-gray in color. The bronchi in some portions of the lung were very much dilated. The microscopic changes in the lungs were about the same as in Dog 4, but there was much more emphysema and the bronchi were more extensively altered and dilated. The second exposure evidently extended these changes in an already diseased lung.

Dog 13.—Short-haired terrier, weighing 8.5 kilos. Under morphin the animal was given several deep breaths of well diluted nitrogen tetroxid. It recovered and at the end of a month was apparently well, but finally began to cough and lose weight, and was killed five weeks after exposure. During the last few days the animal coughed a good deal. At autopsy a lobular bronchopneumonia was found together with the usual emphysema. An atypical pneumococcus was isolated from the pneumonic areas, and the lesion, when examined microscopically, was found to be quite different from that seen in the other dogs, corresponding to that found after bacterial infections. The alveoli were filled with a richly leukocytic exudate, and bacteria could be demonstrated by appropriate stains. The lesion was evidently a spontaneous bacterial pneumonia developing in a lung weakened by the action of the nitrogen tetroxid fumes. Such a pneumonia is not infrequent in animals on whom severe operations have been performed.

PROPHYLAXIS

The chief danger of nitrogen tetroxid lies in the fact that a 1 per cent. mixture of the gas with air can be inhaled without inducing coughing or spasm of the larynx, so that the bronchial and pulmonary epithelium is seriously damaged before severe symptoms supervene. This is quite impossible with chlorin, sulphur dioxid, or ammonia, which cannot be inhaled even in a mixture much diluted with air without causing a spasm of the glottis and suffocation.

As the gas is generated by contact of nitric acid with any organic matter, the straw packing and wooden cases in which the acid carboys are inclosed usually start the reaction, the heat evolved often being sufficient to set the woodwork on fire, thus increasing the difficulty of handling the situation. Nitric acid should, therefore, be stored in an amply ventilated separate building with stone or concrete floor, if possible, and arrangements should be made so that the room can be promptly flooded with water. The handling of the carboys should be

placed in the hands of a few skilled workmen who have been instructed as to the dangers of inhaling the fumes arising when the acid is spilled. Sand is the best material for absorbing any acid which may be upset. If it is necessary for the workmen to enter a room in which the acid has been spilled, their mouths and noses should be covered with cloth moistened with very dilute ammonia.

TREATMENT

There is no satisfactory treatment after the gas has been inhaled. Breathing ammonia vapor has been suggested, but this only adds a second corrosive gas to that already present in the lungs. Oxygen inhalations aid in combating the dyspnea, but do not touch the cause of this symptom, which is chiefly due to the edema of the walls of the bronchi. Morphine and stimulants should be given according to the symptoms.

CONCLUSIONS

1. The inhalation of even small quantities of nitrogen tetroxide gives rise to an exceedingly dangerous pulmonary condition with a characteristic lung lesion both in man and in animals.

2. As there is no satisfactory treatment of the condition it is of the utmost importance that careful instruction be given to all factory laborers or laboratory workers who have to handle concentrated nitric acid as to the dangers incurred and the means of avoiding them.

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An excellent description of the symptoms in poisoning by nitrogen tetroxide with a fair bibliography is to be found in Kunkel: *Handbuch der Toxikologie*, Jena, 1901, p. 282. Pott (*loc. cit.*, note 24) gives references to the older cases. Kobert: *Lehrbuch d. Intoxikation*, 1906, also gives a considerable number of references to the literature, not without the usual inaccuracies. Kockel (*loc. cit.*, note 13) refers to a number of recent cases, and Schubert (*loc. cit.*, note 7) has a fair bibliography and gives important suggestions for prophylaxis. The best bibliography is contained in Witthus and Becker: *Medical Jurisprudence and Toxicology*, 1911, iv, 301, New York.

ORGANIC IODIN PREPARATIONS, THEIR PHARMACOLOGY AND THERAPEUTIC VALUE *

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The introduction within recent years of numerous organic iodine compounds as substitutes for the iodides, the extravagant claims made for some of them by the manufacturers, both as regards therapeutic efficiency and absence of toxic side actions, and the scarcity of literature on the subject in American periodicals seem to demand a review of the entire subject of the value of these substances as therapeutic agents. Most of these compounds have originated from German manufacturers, and nearly all of the investigations regarding them have been published in that country. These substances, however, are being rapidly introduced into the American market, and at the suggestion of the Council on Pharmacy and Chemistry of the American Medical Association, I have undertaken an investigation of the pharmacological basis for the use of such compounds as substitutes for the iodides. The present paper deals chiefly with the literature on the subject.

I.—CLASSIFICATION AND CHEMICAL NATURE

Most of the organic iodine preparations introduced up to the present time as substitutes for inorganic iodides are addition products of iodine with either proteins or unsaturated fatty acids or fats. Other organic combinations of iodine have usually so great an action due to the remainder of the molecule that the iodine action is obscured, and they are as a rule not suitable for administration as substitutes for the iodides.

A. *Iodized Albumins or Proteins*.—The first iodized albumins were prepared by Boehm and Berg.¹ The resulting product could be easily deprived of its iodine by washing with water, or by dialysis, so that the combination between the iodine and the albumin was not firm, and they considered that the iodine was mechanically held. Liebrecht and Roehmann² iodized casein by warming it with iodine. The resultant compound contained no free iodine, but gave off iodine on washing with water and alkalis. Their "Periodcasein" held 17.8 per cent. of iodine, but after washing it left "Iodcasein" with 5.7 per cent. Both compounds split off sulphur and phosphorus easily. Hofmeister³ prepared iodo-albumin from

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1. Boehm and Berg: Arch. f. exper. path., 1876, v, 329.

2. Liebrecht and Roehmann: Arch. f. exper. Path., 1894, xxx, 1824.

3. Hofmeister: Ztschr. f. physiol. Chem., 1897, xxiv, 159.

crystallized egg albumin. Many other iodized proteins are now on the market, and several of them are described below. Most of these preparations no longer give the Millon reaction, and on this account it has been considered that the tyrosin group in the protein molecule has taken up the iodine. To bear this out, a tyrosin-iodine compound (3-5 diiodotyrosin, an iodine complex found in sponges⁴ and other places in nature) has been separated from a number of the iodized proteins by hydrolysis (*vide infra*). Undoubtedly, however, as shown by Oswald⁵ and by Pauly,⁶ other groups in the protein molecule are also involved in the combination, and according to their work it is probable that both histidin and phenylalanin may take up iodine when a protein is iodized. It has been shown that many of the commercial preparations of iodized proteins consist of a mixture of a true compound of iodine with the protein molecule, of inorganic iodide, possibly loosely combined, and in some cases, of free iodine. The nature of the commercial preparations of iodized proteins so far studied may be here briefly summarized. Many of these preparations are not yet on the American market.

COMMERCIAL PREPARATIONS

Iodalbacid (Fabrikanten Herrn Gans in Frankfurt) is a commercial iodized albumin, said to be obtained by electrolyzing an iodide solution in which the anode is surrounded by a protein. It is said to contain 10 per cent. of iodine. Oswald⁷ hydrolyzed this compound and obtained 0.4 gram of diiodotyrosin from 100 grams original substance. Taege⁸ also examined this substance and found it to contain only 5.5 to 5.6 per cent. of iodine. He found it free of inorganic iodine, and found no iodine split off on shaking with water, and concluded that all the iodine is bound in the molecule. When given by mouth he found that 66 per cent. of the iodine was excreted in the urine within eighty hours, 60 per cent. in organic combination and 6 per cent. in inorganic form.

Iodized egg white is manufactured in three forms (Chem. Fabrik von Dieterich in Helfenberg): (1) *Iodeigon* is an iodized, water insoluble, egg albumin, with 20 per cent. of iodine. This compound was studied by Taege,⁸ who found that 95 per cent. of the total iodine was in loosely combined, inorganic form, mainly as hydriodic acid, and this was easily split off on shaking with cold water. On giving this compound by mouth he found that the excretion ended in ninety hours, with the excretion of 76.4 per cent. of the total iodine, with 23.4 per cent. in organic form and 53.0 per cent. in inorganic form. (2). *Iodeigonatrium* is a

4. Wheeler and Mendel: Jour. Biol. Chem., 1909, vii, 1.

5. Oswald: Ztschr. f. physiol. Chem., 1909, lviii, 299.

6. Pauly: Ztschr. f. physiol. Chem., xliii, 2213.

7. Oswald: Ztschr. f. physiol. Chem., 1911, lxx, 311.

8. Taege: Med. Klin., 1910, vi, 1536.

water soluble, sodium salt of an iodized egg albumin, said to contain 15 per cent. of iodine. This compound was examined by Oswald,⁹ who found 96 per cent. of the iodine split off after four and one-half hours' boiling with saturated barium hydrate. He was unable to separate iodotyrosine from this substance. Mosse and Neuberg¹⁰ also examined this compound and found only a little iodine split off on boiling with dilute acids. (3) *Peptoidigon* (iodopeptone), a third form, contains 15 per cent. of iodine. *Iodomangan*, N. N. R., contains 1 per cent. of this compound.

Iodglidin (Klopfer, in Dresden) is an iodized plant albumin (gliadin) containing 10 per cent. of iodine, of which 38.4 per cent. is in loosely combined, inorganic form (Taege). Taege gave this compound by mouth and found 63.2 per cent. of the iodine excreted in seventy-eight hours, with 48.2 per cent. in inorganic form and 15 per cent. in organic combination. Neuberg¹¹ hydrolyzed this compound with 30 per cent. sulphuric acid at 40 C., and separated a crystalline copper salt containing 52.25 per cent. iodine, but he did not obtain diiodotyrosine. Oswald⁷ also hydrolyzed iodoglidin and obtained 7.3 per cent. of the original iodine present as diiodotyrosine, using saturated barium hydrate as the hydrolyzing agent. Wheeler and Mendel¹² also found diiodotyrosine on hydrolysis. According to Broking,¹³ iodoglidin is very unstable, affected by light, pepsin, trypsin, etc. The iodine is firmly combined only in part, and a much greater part is loosely held, this agreeing with the results of Taege. Boruttau¹⁴ showed that iodine could be split off by digestion with pepsin, treating with alcohol, or boiling with acids.

Iodalbin, N. N. R. (Parke, Davis & Co.), is said to be a compound of iodine with blood albumin, containing approximately 21.5 per cent. of iodine. It is said to contain no free iodine, unless decomposed. It is insoluble in the ordinary solvents, but soluble in alkalies. I have examined samples of this substance, obtained in the open market, and find the claims as to the total amount of iodine to be substantiated, as I have found 21.6 per cent. of iodine. The dry substance gives a strong blue color with starch paste. On shaking for a few minutes with a dilute solution of potassium iodide (6 gm. in 500 c.c.) an amount of iodine equivalent to 3.1 per cent. of the original weight of the substance is separated from it. On shaking for four hours in distilled water, at room temperature, I have found an amount of iodine equivalent to 4.9 per cent. of the original weight of the substance to be separated off. The considerable amount of

9. Oswald: Ztschr. f. physiol. Chem., 1911, lxxii, 374.

10. Mosse and Neuberg: Ztschr. f. physiol. Chem., 1902-3, xxxvii, 427.

11. Neuberg: Biochem. Ztschr., xxvii, 251.

12. Wheeler and Mendel: Biochem. Ztschr., 1910, xxix, 419.

13. Broking: Ztschr. f. exper. Path., 1910, viii, 125.

14. Boruttau: Deutsch. med. Wehnschr., 1907, 1490.

free iodine which the substance contains would doubtless prove irritating in the stomach.

Iodomenin (Herr Wölfling, Berlin) is a compound of albumin with the bismuth iodine. It contains 4.45 per cent. of iodine (Taege⁸), and of this 94.4 per cent. is split off by shaking with water, most of it being united to bismuth. Taege gave this substance by mouth, and found 81.4 per cent. of the total iodine given, excreted in ninety hours, 65.7 per cent. inorganic, and 15.7 per cent. inorganic combination.

Proiodin (Wolf, in Bielefeld) is an iodized casein with an iodine content of 4.23 per cent. (Taege⁸), that is firmly bound in the protein molecule. Practically all of this substance is excreted in organic combination.

Iodomaisine is the iodized product of the albumin from corn meal (zein) containing 44.68 per cent. of iodine. It gives both the biuret and Millon reactions.

Iodtropon (Troponwerken in Mülheim) contains 5 per cent. of iodine. Of the total iodine only 3.37 per cent. is split off on shaking with cold water, leaving 96.63 per cent. in organic combination. In sixty hours only 13.2 per cent. of total iodine given was found in the urine (Taege⁸), and at that time the urine was free of iodine.

B. Iodized Fats and Fatty Acids.—The first iodized fat to be recommended for therapeutic use was described by Winternitz.¹⁵ It was introduced into the market under the name of Iodipin (*vide infra*). Since then numerous other compounds have been manufactured, their composition depending on the fact that the free valences in unsaturated fatty acids may be satisfied by iodine. The resulting compounds are generally free from free iodine, and do not yield their iodine readily, except on hydrolysis. They are generally, therefore, more stable than the iodized albumins.

Iodipin, N. N. R. (Merek), is the product of the addition of iodine chloride to oil of sesame. It is on the market in two forms, one of 10 per cent. strength, and the other of 25 per cent. strength, for hypodermic use. The darker color of the 25 per cent. preparation is not due to free iodine, but to a resin-like body which the oil contains.¹⁶

Sajodin, N. N. R. (Farbenfabriken von Elberfeld), is the calcium soap of a fatty acid obtained by iodizing erucic acid, forming iodo-behenic acid. The formula is said to be $(C_{21}H_{42}IOO)_2Ca$. Theoretically this should contain 26.03 per cent. of iodine. Two samples analyzed by me showed an iodine content of 22.46 per cent. and 22.58 per cent. On boiling for fifteen minutes with 25 per cent. sulphuric acid, the substance splits off the iodized fatty acid, which by further hydrolysis yields its iodine.

15. Winternitz: Deutsch. med. Wochenschr., 1897, xxiii, 477.

16. Winternitz: München. med. Wochenschr., 1903 I, 1241.

Lipoidin is a new iodized fatty acid ester described by Loeb and van der Velden.¹⁷ It is the ethyl ester of a diiodized, unsaturated fatty acid of the formula $C_{24}H_{44}I_2O_2$, containing 41.06 per cent. of iodine. It is soluble in 70 per cent. alcohol, also in oils, fats, benzol, chloroform, and insoluble in water.

Iodostarin (Hoffmann-La Roche Chemical Works) is a new diiodized fatty acid of the formula $C_{18}H_{32}I_2O_2$, and should contain 47.5 per cent. of iodine. The Hoffmann-La Roche company has furnished me with sample tablets of the substance, each containing 0.25 grams of the compound, and said to contain 0.12 grams of iodine. In my analysis of these tablets I have found the iodine content to be 46.53 per cent., each tablet containing 0.116 grams. *Iodostarin* occurs as a colorless powder, insoluble in water, but soluble in alcohol, ether, etc.

Iodival (Knoll & Co.) is iodoisovalerianyl urea, corresponding to the bromide compound "Bromural," N. N. R. It is somewhat soluble in water. It is said to contain 47 per cent. of iodine.

C. Other Organic Iodin Compounds.—The other organic iodine compounds used therapeutically are used mainly for their antiseptic action. Iodoform (CHI_3) has, of course, priority over the rest of these. Numerous substitutes for iodoform have been introduced, such as *Thymol Iodid*, U. S. P. (Aristol); *Europfen*, N. N. R.; *Airol*, N. N. R.; *Iodone*, N. N. R.; *Iodoformogen*, N. N. R.; *Vioform*, N. N. R., etc. If these substances are given internally they are split in the body, and the iodine is liberated in the form of iodides, and excreted, but the substances themselves and their decomposition products in the body have certain toxic actions (such as that of iodoform) which render them unsuited for internal use.

Iothin, N. N. R. (Farbenfabriken von Elberfeld Co.), is di-iodo-hydroxy-propane, obtained by chlorinating glycerin and replacing the chlorine by iodine. It is a yellowish, oily, heavy liquid, said to contain 77 per cent. of iodine, and is recommended for application to the skin in the form of inunctions, for absorption.

Glycerodin, N. N. R. (H. K. Wampole), the glycerite of hydriodic acid, is not a true organic preparation.

Iodocitin is a recently described compound of iodine and lecithin.¹⁸

II.—ABSORPTION AND EXCRETION

Since most of the organic iodine preparations used internally are addition products of iodine with proteins or fatty acids, the question of their absorption is intimately concerned with the physiology of the

17. Loeb and Van der Velden: *Therap. Monatsh.*, 1911, xxv, 209.

18. Neuberg: *Therap. d. Gegenw.*, August, 1911.

absorption of the proteins and fats. As certain changes occur in these substances in the process of digestion and absorption, we expect to find that their iodine addition products will undergo certain similar changes in the gastro-intestinal tract. Boruttan¹⁹ has carried on artificial peptic and pancreatic digestion of the iodized proteins, and has determined the amount of iodine present in the splitting products obtained. He found that the compounds which are easily deprived of their iodine by washing, etc. (such as iodoglucosin), yield it readily on digestion, and a relatively large amount appears as inorganic iodide, while a relatively small amount remains in the undigested residue. The reverse is true of the more stable compounds, such as iodalbumin. He found iodine in all the fractions of acid proteins, peptones, etc. He concluded that the splitting off of inorganic iodine did not occur in the stomach, though it could be produced outside the body by peptic digestion, but that the splitting products of the proteins left the stomach before that stage had been reached, and that the process was completed by pancreatic digestion, and that a large amount of the iodine was absorbed in the form of inorganic iodides. V. Fürth and Friedman²⁰ demonstrated that when iodalbumin, one of the more stable compounds, was fed, most of the iodine was carried in the blood in inorganic form. Some absorption of the iodine in the form of iodized splitting products of the proteins also occurs, the amount depending on the amount of iodine which is firmly bound in the protein molecule. As 3-5 diiodotyrosin has been obtained from hydrolysis of many of the iodized proteins, it is probable that a part of the iodine is absorbed in that form, and similar forms. Mosse and Neuberg²¹ found iodhippuric acid in the urine on feeding iodoarginine to rabbits, and found iodbenzoic acid in the blood on feeding the same substance to dogs. Oswald²² was unable to confirm their results, and concludes that the iodine in the preparation used was not held as diiodotyrosin.

The form in which the iodine, fed in the form of iodized proteins, is excreted depends largely on the form in which it is absorbed. Taegert²³ has shown a close parallelism to exist between the stability of the iodized proteins and the amount of organic iodine in the urine. It is probable, therefore, that a large part of the iodine absorbed in organic combination is excreted in practically the same form, without ever being liberated in inorganic form. This is borne out by the work of Oswald,²³ who fed 3-5 diiodotyrosin to rabbits, and found that about half of the iodine given was

19. Boruttan: *Ztschr. f. exper. Path. u. Therap.*, 1910, viii, 418.

20. Von Fürth and Friedman: *Arch. f. exper. Path., Festschr. f. Schmiedeberg*, 1908, p. 214.

21. Mosse and Neuberg: *Ztschr. f. physiol. Chem.*, 1903, xxxvii, 419.

22. Oswald: *Ztschr. f. physiol. Chem.*, 1910, lxx, 141.

23. Oswald: *Ztschr. f. physiol. Chem.*, 1909, lxvii, 399.

excreted in the urine in organic combination, partly in the same form in which it was given. This iodine would necessarily, therefore, be devoid of any iodine "ion action." Abderhalden and Slavu²⁴ gave 3-5 diiodotyrosin by mouth and subcutaneously and found most of the iodine in the urine in inorganic form. They found some in organic combination, but not as diiodotyrosin. They found, however, a considerable amount of diiodotyrosin in the feces, even when the substance was given subcutaneously.

The fate of the iodized fats is similar to that of the fats and fatty acids themselves. They generally pass through the stomach unchanged²⁵ and are split in the intestines and absorbed. In the case of sajodin, the calcium is probably first split off, as this change occurs first on hydrolysis, and following this there is at least partial splitting off of the iodine from fatty acid. Metzger²⁶ fed sajodin to dogs with intestinal fistulæ, and showed the presence of inorganic iodine in the duodenum during digestion. With iodipin he was unable to demonstrate any inorganic iodine in the stomach or upper duodenum. According to Winternitz,¹⁶ iodipin is not absorbed in the stomach, but is split in the intestines by the bile and pancreatic and intestinal juices, leaving the iodine bound to the fatty acid, and is absorbed mainly as the iodized fatty acid. He showed that the iodine was present in the ether extract of the blood after absorption, and concluded that it was identified with the fats there. By oxidation of the iodized fatty acid in the blood and in the tissues the iodine is split off in the form of iodide and excreted. Wells²⁷ concluded that when iodipin was injected subcutaneously it was carried in the blood mainly as inorganic iodine. Boruttan¹⁹ gave sajodin and iodival in large doses to dogs, took blood from the carotid, and found that much more iodine was present in the blood in inorganic than in organic form. Abderhalden and Kautzsch²⁸ concluded that sajodin was absorbed as the mono-iodobehenic acid, and was taken into the cells in that form, and that iodine was liberated by oxidation in the cells. My analysis of the liver after giving sajodin (*vide infra*) would indicate that a part of the iodine is present in the tissues as the iodized fatty acids, though I do not regard this as sufficiently demonstrated.

Loeb and van der Velden¹⁷ showed that iodival is absorbed without any inorganic iodine being split off in the intestine. Broking¹³ came to the same conclusion.

24. Abderhalden and Slavu: *Ztschr. f. physiol. Chem.*, 1909, lxi, 405.

25. Posternak, *Bull. Soc. de therap.*, series 4, 1910, xi; *Bachem: München. med. Wehnschr.*, 1911, No. 41.

26. Metzger: *Med. Klin.*, 1911, vii, 1390.

27. Wells: *Ztschr. f. physiol. Chem.*, 1905, xlv, 412.

28. Abderhalden and Kautzsch: *Ztschr. f. exper. Path. u. Therap.*, 1907, iv, 1.

When the iodized fats are taken the greatest amount of iodine leaves the body in the urine in the form of potassium iodide,²⁹ though a small amount is present in the urine in organic combination. This is of no significance, as about 9.9 per cent. of iodine given as potassium iodide may appear in the urine in organic combination (Taeger⁸), and Harnack³⁰ has shown that a spontaneous change from iodide to organically combined iodine may occur under normal circumstances in fresh urine.

The excretion of iodine in the milk, when given in the form of iodized fats, is of interest. Löns³¹ fed lipoiodine and found greater amounts of iodine in the milk than when corresponding amounts of potassium iodide were fed. He was unable, however, to identify the iodine in the milk with the milk fat. Winternitz¹⁵ fed iodized hog fat to a goat, and found iodine in the milk in the form of an iodized milk-fat, and also in the milk serum in inorganic form. In seven days 6.2 per cent. of iodine given was excreted in the form of iodized milk-fat.

The absorption of iodine compounds from other places than the gastrointestinal tract has been studied. The absorption of iodipin when administered subcutaneously has already been mentioned. Winternitz¹⁹ showed that iodipin was not absorbed through the unbroken skin, as the urine remained iodine-free, and he also showed that not over 10 per cent. was absorbed when administered by rectum. Iothion, which is of the nature of an iodized volatile oil, is rapidly absorbed through the unbroken skin,³² appearing in the urine in about one hour. It is irritant to the skin, and is usually applied in the form of an inunction, using lanolin as a base.

RATE OF ABSORPTION AND EXCRETION

The rate of absorption and excretion of the organic iodine preparations has been studied mainly in comparison with the excretion of potassium iodide. The excretion of potassium iodide has been studied by many observers, and the results agree in general with those of Anten,³³ who showed that (1) after one dose of potassium iodide (0.5 grams) the highest amount in the urine is in the second hour, rarely in the first or third; (2) the average amount excreted in the urine after this dose is 75 per cent. (minimum, 65 per cent., maximum, 85 per cent.); (3) the duration of the presence of iodine in the urine after such a dose of 0.5 grams is forty hours. After two doses five hours apart the duration is fifty-six hours, and after three doses in ten hours is seventy-seven hours; (4) when mucilaginous bodies are given with potassium iodide the excre-

29. v. Klingmüller: *Berl. klin. Wehnschr.*, 1899, p. 540; Winternitz: *München. med. Wehnschr.*, 1903, I. 1241.

30. Harnack: *Arch. internat. d. Pharm. u. Therap.*, 1910, xx, 247.

31. Löns: *Berl. klin. Wehnschr.*, 1911, xlviii, 2064.

32. Kellermann: *Ztschr. f. exper. Path.*, 1905, ii, 416.

33. Anten: *Arch. f. exper. Path. u. Pharm.*, 1902, xlviii, 331.

tion is slower in the first two hours; (5) when potassium nitrate or sodium chlorid is given with potassium iodid the excretion of iodine is distinctly greater. Broking¹³ found potassium iodid to be rapidly absorbed in the small intestine and the excretion in the urine to average 80 per cent. of that given. Excretion begins a few minutes after taking, and lasts in the urine sixty hours as a maximum. He found 75 per cent. excreted in the urine in the first twelve hours, and only 5 per cent. after that time, and found iodine in the feces only in traces. The relation between the excretion of chlorine and iodine, and particularly between chlorine and bromine has been studied by a number of observers. Sarvonat and Crenieu³⁴ have shown that animals on a chlorine free diet retain iodine in the tissues longer and in greater amounts than those receiving chlorides in the diet. The fate of the iodine which does not appear in the urine has not been entirely settled. Only small amounts appear in the feces, but iodine has been found in the perspiration, and in the hair, etc., and the thyroid may hold a considerable amount (*vide infra*). Boruttau¹⁹ found small amounts in the intestine, kidneys, heart and lungs four days after giving potassium iodid to a rabbit.

The iodized fats and fatty acids show the greatest difference from potassium iodid with regard to rapidity of excretion. After the administration of sajodin the iodine does not appear in the saliva and urine until after one to three hours, and eighty-four hours is required for excretion of iodine in the urine after a single dose, during which time 35 to 50 per cent. of iodine given appears in the urine (Broking¹³). From 7 to 10 per cent. appears in the feces unchanged. The highest point in the excretion is reached in the first twelve hours, but the amount excreted remains high during the first thirty-six hours, though in the case of potassium iodid it falls very low after twelve hours. Singer³⁵ found only 58.5 per cent. of iodine given as iodipin in the urine, and showed that the excretion was much slower than in the case of potassium iodid. Broking¹³ showed that the excretion of iodival began rapidly, reached its height within a few hours, and continued about sixty hours after a single dose, resulting in the excretion of about 80 per cent. of the iodine given. He showed that the rate of excretion was somewhat more uniform than with potassium iodid, especially when the drug was given in successive doses. He found 2 per cent. remaining in the feces. Loeb and van der Velden¹⁷ showed that iodival is rapidly absorbed and appears in saliva and urine in twelve minutes, and that the rate of excretion is practically parallel with potassium iodid. Loeb and van der Velden also showed that with lipoiodin the excretion began in two to three hours, and continued seventy-two to 120 hours, and they found an average of 3 to 12 per cent. in the

34. Sarvonat and Crenieu: *Compt. rend. Soc. de biol.*, 1911, lxx, 268.

35. Singer: *Ztschr. f. klin. Med.*, 1904, lii, 521.

feces under normal conditions. They also found some of the iodine present in the blood in ether-soluble form, and concluded that the ester or the free fatty acid was absorbed with iodine combined. Abderhalden and Hirsch³⁶ found that the ethyl esters of iodized fatty acids, such as lipiodine, were slowly absorbed. Loeb and van der Velden concluded that when lipiodine was given the iodine was slowly and evenly split off, giving a comparatively even iodine effect.

The iodized proteins, being of a more or less unstable character, are generally absorbed and excreted more rapidly than the iodized fatty acids, and the rate of excretion is more nearly like that of potassium iodide. Broking¹³ found iodoglucine to be excreted in a similar manner to iodine, and found 3 to 4 per cent. in the feces. I have found iodine in the urine within fifteen minutes after the administration of iodalbumin, which would be expected from its content of free iodine. The work of Taege, showing the relationship between the stability of the iodized proteins, has already been quoted (*vide supra*).

Metzger²⁶ studied the excretion of iodocitin (iodized lecithin) and found the highest point in excretion within the first twelve hours, a considerable amount being excreted in organic form.

The relation between iodine and chlorine excretion has been shown by Herzfeld and Heimann³⁷ to be the same in the case of iodostarin as when the iodides are given.

The influence of pathological conditions on the absorption and excretion of certain compounds has been studied by Loeb and van der Velden,¹⁷ who showed that in patients with diarrhea, 50 per cent. of iodine given as lipiodine may appear in the feces. Van der Velden³⁸ found that the excretion of iodine in the urine may be markedly changed from normal under certain pathological conditions. He found that there was a slowed excretion of potassium iodide, but a quickened excretion of iodine, and concluded that there may be a more rapid and intensive splitting of the iodine from the organic complex in the one case. The lessened excretion of iodine in nephritis has also been shown in the case of iodine by Norsa and Arcadi.³⁹

III.—DISTRIBUTION IN THE BODY

The factors concerned in the entrance of the various iodine compounds into the cell are still unsettled. O. Loeb⁴⁰ gave potassium iodide to rabbits, and found the largest amounts of iodine in the blood, kidneys and lymph-nodes (exclusive of thyroid). He found the brain, spinal cord, fatty tissues and bone always iodine-free. When he gave iodine, iodaniline and

36. Abderhalden and Hirsch: *Ztschr. f. physiol. Chem.*, 1911, lxxv, 38.

37. Herzfeld and Heimann: *Med. Klin.*, 1911, vii, 1858.

38. Van der Velden: *Therap. Monatsh.*, 1910, xxiv, 632.

39. Norsa and Arcadi: *Zentralbl. f. Biochem.*, x, 619.

40. Loeb, O.: *Arch. f. exper. Path.*, 1907, lvi, 310.

iodoform he found iodine in the brain and in fatty tissues, and he ascribed their entrance into these tissues to their lipoid solubility. Boruttau⁴⁰ was unable to confirm his results with regard to potassium iodide, as he found iodine in the brain after giving potassium iodide. Boruttau found, four days after giving iodized proteins, that the largest amounts of iodine were in the brain. He concludes that the "Neurotropie" and "Lipotropie" of Loeb are relatively unimportant, except for iodized fats subcutaneously injected.

In this connection it is important to know in what form the iodine is present in the tissues. Lesser⁴¹ gave a rabbit 10 c.c. of 25 per cent. iodipin within twenty-four days, separated the fats from the tissues by ether extraction and obtained the following results:

Organ	Weight	— Mg. per Gram of Organ —	
		Total Iodin	I as Iodized Fat
Lung	26.4	0.55	0.255
Liver	68.0	0.45	0.1
Kidneys	18.2	0.2	0.009
Mesenterial fat	4.0	0.045
Blood	100 c.c.	0.15	trace

He concluded that on giving iodized fat a large amount of iodine was split off, and only a part circulated in the blood as fat or fatty acid, while a part is taken up by the tissues in the form of the fat or fatty acid.

To determine with what constituents of the cell the iodine is mainly identified after entrance into the tissues, I have analyzed certain tissues for the distribution of iodine in the cell, after giving iodized fatty acids, iodized proteins and potassium iodide. The liver was chosen for this work, as it is of convenient size (in rabbits) for extraction, and because it contains a considerable amount of lipoid substance, and also because it takes up a considerable amount of iodine. The separation of the cell constituents was made by the method described by W. Koch.⁴² The rabbits were given the iodine compound hypodermically or by stomach tube, and were later killed by bleeding from the neck, and the tissues collected and estimations of the total iodine in the principal organs made. The liver was cut up in small pieces and put in enough absolute alcohol to make 85 per cent. alcohol, with the water in the tissue, and allowed to stand for one to two weeks, after heating up to 70 C. for about an hour. It was then subjected to a continuous hot alcohol extraction in the extraction apparatus described by Koch, for four hours, followed by an ether extraction of one hour. The dried residue was then finely powdered, soaked up with water, made up again with absolute alcohol to 85 per cent. alcohol and allowed to stand a few hours, after which it was again extracted with hot alcohol for about twelve hours. The residue was then dried in

41. Lesser: Arch. f. Dermatol. Syph., 1903, lxiv, No. 1.

42. Koch, W.: Jour. of Am. Chem. Soc., 1909, xxxi, 1330.

an oven to constant weight. The alcohol extract was evaporated to near dryness, dried for two to three days in a vacuum desiccator and emulsified in water. After complete emulsification the lipoids were precipitated according to the method of Koch,⁴² by hydrochloric acid and chloroform. Estimations were made of the amount of iodine in the three fractions separated in this way ((1) protein residue, (2) lipoids—alcohol soluble, water insoluble, (3) water soluble, alcohol soluble). All iodine determinations were made by a slight modification of the method described by Hunter.⁴³ This method has given very uniform results in our hands.

The protocols of typical experiments will serve to illustrate the results.

Experiment V.—Potassium Iodid—Rabbit, weight 1.600 gm.

July 22, 3 p. m., 0.8 gm. KI in water by stomach tube.

July 23, 9 a. m., 0.5 gm. KI in water by stomach tube.

July 23, 10:30 a. m., killed by bleeding from neck.

Analysis of Tissues

Organ	Weight, Fresh, gm.	Mg. I per Gram Fresh Tissue
Kidneys	10.1	0.344
Blood	47.1	0.292
Heart	4.15	0.122
Liver	65.95	
Protein residue	0.000	
Lipoid (alc. sol., water insol.)	0.032 (32.0%)	
Alcohol soluble, water sol.	0.067 (67.0%)	
Total		0.099
Brain	8.95	0.007

Experiment VI.—Iodalbumin—Rabbit: weight 1.600 gm.

July 25, 3:00 p. m., 2 gm. iodalbumin in NaHCO₃ sol. by stomach tube.

July 26, 11:45 a. m., 2 gm. iodalbumin in NaHCO₃ sol. by stomach tube.

July 26, 2:00 p. m., killed by bleeding from neck.

Analysis of Tissues

Organ	Weight, Fresh, gm.	Mg. I per Gram Fresh Tissue
Kidneys	9.7	0.21
Blood	63.7	0.209
Heart	4.0	0.116
Liver	70.45	
Protein residue	0.000	
Lipoid (alc. sol., water insol.)	0.014 (24.5%)	
Alcohol sol., water sol.	0.043 (75.4%)	
Total		0.057
Brain	8.25	0.008

Experiment II.—Sajodin—Rabbit; weight 1.790 gm.

June 24, 0.3 gm. sajodin in olive oil subcutaneously.

June 25, 0.3 gm. sajodin in olive oil subcutaneously.

June 26, 9:30 a. m., 0.5 gm. sajodin in olive oil subcutaneously.

June 26, 1:30 p. m., killed by bleeding from neck.

43. Hunter: Jour. Biol. Chem., 1910, vii, 321.

Analysis of Tissues

Organ	Weight, Fresh, gm.	Mg. I per Gram Fresh Tissue
Heart	4.6	0.0276
Kidneys	10.82	0.0257
Lungs	9.12	0.0185
Liver	54.9	
Protein residue	0.0000	
Lipoid (alc. sol., water insol.)	0.0106 (62.7%)	
Alcohol sol., water sol.	0.0063 (37.3%)	
Total		0.0169
Blood	74.7	0.0151
Spinal cord	2.7	0.0078
Brain	7.85	0.0053

Experiment IV.—Sajodin—Rabbit; weight 1,400 gm.

July 17, 2:10 p. m., 2 gm. sajodin in olive oil by stomach tube.

July 18, 9:30 a. m., 2 gm. sajodin in olive oil by stomach tube.

July 18, 1:30 p. m., killed by bleeding from neck

Analysis of Tissues

Organ	Weight, Fresh, gm.	Mg. I per Gram Fresh Tissue
Heart	3.2	0.178
Liver	49.5	
Protein residue	0.010 (6.4%)	
Lipoid (alc. sol., water insol.)	0.082 (52.9%)	
Alcohol sol., water sol.	0.063 (40.6%)	
Total		0.155
Blood	26.5	0.125
Kidneys	8.3	0.102
Brain	6.05	0.026

The results of these experiments would tend to show the following:

1. There are no essential differences in the distribution of iodid after giving potassium iodid and iodalbin, either in the distribution between the different organs, or in the distribution in the various constituents of the cell.

2. Sajodin produces a relatively higher percentage of iodine in the lipid fraction, indicating that the lipoids of the cell take up iodized fats from the blood. (More data are required on this point.)

3. The relative amount of iodine in the nervous tissues after sajodin is much greater than after potassium iodid or iodalbin — though small amounts of iodine have been found in all cases. The liver also stands relatively higher in iodine content after sajodin.

IV.—PHYSIOLOGICAL ACTION

The question of the physiological action of the organic iodine preparations is even more complex than that of the inorganic iodids, about which we know relatively little. In the case of potassium iodid, we have to consider the action of the salt itself, its *ions* after dissociation, and the free iodine which may be liberated in the body. In the case of an iodized

fat or protein we must consider the action of the molecule as a whole, its organic splitting products, the action of the iodine after liberation from the molecule and recombination in organic or inorganic form in the body. The last-named action would probably be identical with the action of iodine given in inorganic form. O. Loeb⁴⁴ divides the consideration of iodine action into three groups: (1) salt action, (2) effects on physiologic activity of thyroid and (3) changes produced in pathologic conditions. He assumes that iodism is due to the flooding of the organism with iodine ions by rapid absorption of potassium iodide, and advocates the use of iodized fats (lipiodine) since the iodine is gradually split off and "flooding" is avoided.

Erlenmeyer and Stein⁴⁵ conclude that all iodine action is *ion* action; that organic iodine compounds act only as iodine is split off in the body, and that such substances as iodipin and sajodine, by their smaller iodine content, are weak substitutes for potassium iodide. They regard iodism as an undesirable side action of *ion* action. Winternitz,⁴⁶ however, maintains that it has not been shown that the action of all iodine preparations is due entirely to *ion* action, or that iodipin and sajodine must be changed into potassium iodide to act, and he claims that iodism is much less frequent with the iodized fats. His contention is undoubtedly true, in that we may have other actions from iodized fats than the iodine *ion* action; but we have no evidence that the action so produced is the action desired in the cases in which the drugs are recommended as substitutes for potassium iodide.

With regard to the question of iodism, v. Notthaft⁴⁷ concluded that the diminution in frequency of observation of iodism with the organic iodine preparations was always associated with other disadvantages, or that they had a feebleness of activity, and the substances either split off too little iodine, or split it off with greater difficulty.

The relation of iodine content to thyroid activity has been known since Baumann⁴⁸ published his observations on the iodine content of the gland. Up to the present time the nature of the iodine complex in the gland is not known. Hunt and Seidell⁴⁹ attempted to find thyrotropic iodine compounds, testing them physiologically by the aceto-nitrile test. The only iodine compound, except that obtained from thyroid, shown to have any specific "thyroid" action was that from "bladderwrack," and that was much weaker in proportion to its iodine content than the thyroid

44. Loeb, O.: *Deutsch. med. Wochenschr.*, 1911, xxxvii, 1006.

45. Erlenmeyer and Stein: *Therap. Monatsh.*, 1909, xxiii, 133.

46. Winternitz: *Therap. Monatsh.*, 1909, Part 8.

47. Von Notthaft: *Monatsh. f. prakt. Dermat.*, Oct. 15, 1910; abstr. in *Jour. Am. Med. Assn.*, lvi, 685.

48. Baumann: *Ztschr. f. physiol. Chem.*, 1895, xxi, 319.

49. Hunt and Seidell: *Jour. Pharm. and Exper. Therap.*, 1910, ii, 15.

substance itself. All other organic compounds studied were found to be relatively only about as active as potassium iodid, and they ascribe their action to their indirectly increasing the activity of the thyroid by increasing its iodine content. V. Fürth and Schwartz⁵⁰ tested the action of iodized egg albumin when administered intravenously and found an action similar to that of iodothyronin, i. e., it produced a fall in blood-pressure both before and after sectioning the vagi. No other thyroid activity, however, has been shown for it.

The giving of iodine in combination with other substances may sometimes lead to toxic action due to the rest of the molecule. This has already been pointed out for iodoform and its substitutes. Other substances, however, intended for use for their iodine content have shown a toxicity far greater than that of potassium iodid. Eeckhout⁵¹ has shown iodoval to have a hypnotic action, similar to that of bromural. Loeb and van der Velden⁵² have shown that iodoval is fatal to rabbits in doses of 0.5 gram per kilo weight. It is obvious, therefore, that such toxic compounds could not be used where the action of large amounts of iodine was desired. Boulaire⁵³ tested the comparative toxicity of various iodine compounds and found the iodized fats least toxic, both as to immediate and late effects, while he found iodothion most toxic. (Iodoval was not tested.)

V.—CLINICAL REPORTS

As is to be expected, we have numerous reports of the use of various organic iodine preparations in practically every disease in which iodine or the iodids are recommended. Many writers have claimed that iodism is less frequent when an iodized fat, for example, is used in place of potassium iodid. We find, however, that in nearly every case these substances have been given in relatively small doses, and very few attempts have been made to increase the dose rapidly, as is often done with potassium iodid. One reason for this is undoubtedly the almost prohibitive cost of the organic preparations, when large amounts are desired.

Many observers have also shown that the stomach is less apt to be disturbed by the administration of organic compounds. This is to be expected when substances not acted on by the gastric contents are given, when the substances are not irritating themselves. In the case of commercial preparations containing free iodine we should not expect them to pass through the stomach without local effect.

Winternitz,⁵⁴ O. Loeb⁵⁵ and Boruttau⁵⁶ agree that the organic iodine preparations are not to be regarded as substitutes for the alkaline iodids in every case, but that each class of compounds has its own special con-

50. Von. Fürth and Schwartz: *Pflüger's Arch.*, v. 125, p. 113.

51. Eeckhout: *Arch. f. exper. Path. u. Therap.*, 1907, lvii, 338.

52. Boulaire: *Compt. rend. Soc. de biol.*, 1906, lvi, 303.

53. Boruttau: *Deutsch. med. Wehnschr.*, 1911, No. 43, p. 1975.

siderations which should be taken into account in the use of any of them. Winternitz¹⁶ recommends the use of iodipin in such cases as bronchial asthma, arteriosclerosis (luetie endarteritis) and lead-poisoning, on account of its slow splitting and prolonged excretion, and states that its use in special cases is well founded. The same considerations also apply to the other members of the iodized fat and fatty acid group, according to their relative rates of absorption, and excretion. We have less physiological grounds, however, for the giving of iodized proteins.

VI.—CONCLUSIONS

From the evidence presented above as to chemical nature, absorption and excretion, distribution, physiologic action and clinical results, we may draw the following conclusions with regard to the therapeutic uses of the organic iodin compounds:

1. Up to the present it has not been shown that the organic iodin preparations, with the exception of preparations of thyroid, have any specific action in pathologic conditions, except the action of iodin after separation from the molecule.

2. The iodized proteins seem to be of advantage for therapeutic use only in so far as they avoid gastric irritation. The more stable compounds are apparently not entirely split in the body and are therefore not well utilized, while the less stable compounds have no advantages over the alkaline iodids, either as to local effects, or as to rapidity of absorption and excretion.

3. The iodized fats and fatty acids appear to have some advantage when the continuous action of small amounts of iodin is desired. They are more slowly and evenly split, and the amount of available iodin in the blood does not vary from time to time to the extent that it does when the alkaline iodids are administered. The use of the iodized fats in such conditions as arteriosclerosis, bronchial asthma, lead-poisoning, etc., probably has some rational basis, therefore, on physiologic grounds. These substances are also as a rule non-irritant to the stomach.

4. The difference in frequency of iodism is probably due to the difference in the amount of available iodin present in the body at any one time. When large amounts of iodin are desired, as in cerebrospinal syphilis, avoiding the danger of iodism would be at the sacrifice of therapeutic efficiency.

5. The use of organic iodid preparations with toxic side actions, due to the molecule or its splitting products, should of course be discouraged. The products of iodin with the higher fats and fatty acids are generally free from toxic actions.

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THE GLYCYLTRYPTOPHAN (PEPTID) SPLITTING AGENT IN HUMAN SALIVA *

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Rather more than a year since, Warfield¹ claimed the discovery of a new enzyme in human saliva, "a substance which has the power to split glycytryptophan" (a dipeptid). This hydrolyzing property of saliva was stated as being lost when saliva is acid or when heated to 100 C. Warfield's report bases his conclusions on the action on glycytryptophan of twenty-eight specimens of saliva. Of this number, saliva was alkaline (where stated) in all the positive reactions and acid in all negative glycytryptophan tests. The use of tobacco, observed in seven instances, did not materially alter the result so long as the salivas remained alkaline.

About six months after Warfield's communication, Weinstein,² in writing of the "tryptophan" test for carcinoma ventriculi, confirmed Warfield's findings. Weinstein's observations are indefinitely stated. The few experiments actually quoted admit of dubious conclusions (*vide* 1 to 3, and A-B). In a footnote Weinstein states that his colleague, Professor Gies, "although suggesting the probability of ereptic and tryptic excretion by the salivary glands, thinks it possible also that the tryptophan producing enzyme in mixed saliva is derived in part from the bacteria in the mouth, especially from cavities in carious teeth."

Previous to Warfield's report, ptyalin (diastase) had been considered the essential enzyme in human saliva. Maltase can hardly be regarded as distinctive. It would seem that if human saliva contain a proteolytic enzyme, new problems in the physiology of digestion would be presented.

The observations included in this report were made in the endeavor to determine the existence of the peptid-splitting agent in saliva, the nature of this agent and the conditions under which it might be evidenced.

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*From the Division of Gastro-Enterology, Mayo Clinic.

1. Warfield: Bull. Johns Hopkins Hosp., May, 1911.

2. Weinstein: Jour. Am. Med. Assn., 1911, lvii, 1420.

AUTHOR'S STUDY

Three hundred thirty-four individuals furnished the specimens of saliva. They were of both sexes and ranged in age from 18 to 74 years. Three hundred eighteen specimens came from patients who presented themselves for test-meal examination of gastric function at St. Mary's Hospital (Mayo Clinic). Sixteen specimens came from laboratory assistants, nurses and physicians.

Collection of Saliva.—In the test-meal cases, patients were fed the Ewald breakfast. From ten to twenty minutes after they had eaten they were furnished with large test-tubes, into which they spat. They were instructed to furnish saliva and not nasopharyngeal accumulations or laryngo-bronchial sputum. The collecting test-tubes had previously been boiled in distilled water, hot air dried and plugged with sterile cotton. Saliva was collected for from forty-five minutes to one and one-half hours following the ingestion of the test meal. It was kept at room temperature in the test-tubes, securely plugged, until the various experiments to be made with it were set up. Except in special instances (*vide infra*) experiments were set up within four hours following the collection of the specimens. The reaction of the saliva was always ascertained with wet litmus at the time the test mixtures were made. In each donor, the teeth, gums, and oral, nasal and pharyngeal mucosae were inspected.

Routine Procedure for Observation of the Peptid-Hydrolyzing Property of Saliva.—For testing the cleavage power of the specimens, the dipeptid, glycyltryptophan, was chosen. The preparation made under the direction of Neubauer and Fischer was used. (Manufactured by Kalle & Co., Biebrich am Rhein, and secured through Noyes Bros. & Cutler, St. Paul, Minn.) This was obtained in small bottles and preserved under an ample layer of toluol. To guard against the crystallization out of the glycyltryptophan from solution, and the consequent doubtfulness of the results, the preparation was kept in a thermostat at 37 C.

The tests were, in general, set up as follows: Into each of a series of sterile test-tubes (those measuring 10 cm. by 14 mm. were found to answer very well) were poured, respectively, 0.3 c.c. of the glycyltryptophan solution, 3 c.c. of saliva and 0.5 c.c. of toluol. Sterile pipets were used in measuring the quantities. In each series controls were set up consisting of (a) 0.3 c.c. glycyltryptophan solution + 3 c.c. sterile distilled water + 0.5 c.c. toluol; and (b) 3 c.c. saliva + 0.5 c.c. toluol. The tubes were inverted several times to secure complete mixture of the ingredients. They were then placed in a thermostat at 37 C. for twenty-four hours. From each tube was next transferred to each of a set of small test tubes, 2 c.c. of the mixture below the toluol layer. To each tube was then added 0.2 c.c. of a 3 per cent. glacial acetic acid in distilled water solution. The tubes were shaken vigorously. Test for free tryptophan was then made. Bromin vapor was allowed to flow into each test-tube until the glass above its contents showed strong amber. The tubes were next shaken and note made of any color change occurring in the mixture. The presence of tryptophan was considered proven when the liquid took on lilac, rose-pink, purple or magenta hues. The color changes were observed by daylight against a white background (filter paper). By this procedure, small amounts of free amino-acid (tryptophan) are readily detected. Questionable reactions were usually due to the presence of very small amounts of tryptophan, dirty saliva, excess of bromin (as when bromin water is used instead of bromin vapor) or poor light.

1. *The Presence of Peptid-Splitting Agent in Whole Saliva.*—In this series of tests a portion of saliva free from food particles, blood or nasopharyngeal mucus was examined first for free tryptophan. Reference to

Table 1 shows that of 334 specimens of saliva, but three showed free amino-acid before the dipeptid glycytryptophan had been added or the specimens had been incubated. All three positive tests were returned by dirty saliva from individuals with pyorrhea alveolaris and many decayed teeth. One individual had enlarged tonsils with ragged crypts filled with creamy exudate. Of the three positive tryptophan tests, two occurred in very acid saliva and one in neutral saliva (case with foul tonsils).

In this same series portions of the saliva (334 specimens) were incubated with glycytryptophan under toluol for twenty-four hours, as described above, and at the end of the incubation period were tested for free tryptophan. Table 1 shows the results.

It will be noted that irrespective of the reaction of the different specimens, 314, or 94.1 per cent., manifested some degree of hydrolytic power for glycytryptophan. Twenty, or 5.9 per cent., were negative, irrespective of reaction of the saliva. We shall comment on the significance of reaction below. It, however, seems proper here to call attention to the facts that of 334 specimens, 148 were neutral to wet litmus, and that of this number 139 (93.9 per cent.) revealed free tryptophan after incubation. Acid reaction was shown by 163 specimens. Of these, 156 (95.7 per cent.) were capable of splitting glycytryptophan. Of the twenty-three distinctly alkaline salivas, nineteen (82.6 per cent.) showed free tryptophan after incubation with the test dipeptid. In view of the difficulty in accurately determining shades of difference in reaction between the neutral and alkaline salivas with litmus, we may fairly group the results from such specimens; in other words, of 171 specimens (neutral and alkaline) 154 (90.+ per cent.) were able to hydrolyze glycytryptophan with resultant detectable amounts of free amino-acid.

Warfield's tabulation of twenty-eight specimens of saliva shows that in his series thirteen were from individuals affected with some form of gastro-intestinal anomaly, while the remainder were from subjects in good health. In twenty-five specimens (89.3+ per cent.) he obtained cleavage of glycytryptophan (bromin water test). He states that all positive reactions were from individuals with alkaline salivas. We are unable to account altogether for the discrepancy between his figures and ours.

TABLE 1.—THE PEPTID-SPLITTING POWER OF WHOLE SALIVA

No of Cases.	Positive Reactions*			Neg. Reactions.	Trypto-phan Test.	Reaction of Saliva.	Percentage.
	+	++	+++				
148	23	64	52	9	1	Neutral	Pos. 93.9 Neg. 6.1
163	27	79	50	7	2	Acid	Pos. 95.7 Neg. 4.2
23	3	3	13	4	0	Alkaline	Pos. 82.6 Neg. 17.3+
334	53	146	115	20	3		

*Degree of reaction: Lilac = +; rose-pink = ++; rose-purple = +++.

Total Pos. (all degrees) = 314 or 94 per cent.

Total Neg. (all degrees) = 20 or 5.9+ per cent.

2. *The Effect of Centrifugalization on the Peptid-Splitting Power of Saliva.*—Portions of 204 salivas were centrifugalized in a motor-driven centrifuge for sixty minutes. Two c.c. of the top layer of each specimen were mixed with glycytryptophan and incubated under toluol for twenty-four hours. Table 2 shows in detail the results.

Several interesting facts are brought out. It will be observed that irrespective of the reaction of the salivas, of the 204 specimens, 167 (81.8 per cent.) showed some hydrolyzing power. This is rather more than 12 per cent. less than was exhibited by non-centrifugalized salivas (Table 1). Thirty-seven (18.1 per cent.) specimens were negative. Table 2 also shows that the degree of reaction is less marked than where non-centrifugalized saliva is tested. The majority of the reactions were + or ++ in this series.

The relation of the reaction of saliva to its peptid-splitting power in this series shows interesting variations from that exhibited in Table 1. Of the ninety-two specimens noted as neutral, seventy-three (78 per cent.) showed hydrolyzing power, while nineteen (21 + per cent.) did not. Of 106 acid salivas, ninety-two (85.8 per cent.) split glycytryptophan and fifteen (14.1 + per cent.) were unable to do so. Of the six distinctly alkaline salivas, three (50 per cent.) split the dipeptid. Combining the results returned by alkaline and neutral salivas, we observe that of a total of ninety-eight specimens, seventy-six (77.5 per cent.) showed hydrolytic power.

In this series of 204 specimens, only one (acid in reaction) gave a positive tryptophan test before incubation. This saliva came from a very foul mouth and contained macroscopic blood and much cellular detritus.

3. *Consideration of Relation of Reaction of Saliva to its Peptid-Splitting Power.*—It is commonly stated that the reaction of saliva is alkaline or neutral to litmus. Using litmus paper moistened in sterilized distilled water, we have found it extremely difficult to determine the finer variations in reaction between weakly alkaline and neutral salivas. Consequently only when there was blue coloration of test paper in the estimation of at least two observers have we called salivas alkaline. Table 1 shows that of 334 specimens of whole saliva, 171 (51.1 per cent.) were neutral or alkaline. Of these 154 (90. + per cent.) split glycytryptophan. One hundred sixty-three (48.9 per cent.) were distinctly acid to wet litmus. Of these, 156 (95.7 per cent.) were hydrolytic for the test dipeptid.

The number of acid salivas was surprisingly large in view of text-book analyses. We suggest that this high proportion of acid reactions may be due to the conditions of the oral cavities of the donors. Many of our patients were adult or aged peasantry from the northwest United States and Canada. There was a considerable percentage of individuals of

European extraction. In many, teeth, gums and nasopharyngeal anomalies had been entirely neglected. Decayed teeth, pyorrhea alveolaris, soggy, oozing tonsils and foul nasal and pharyngeal mucosa were common (*vide infra*). It is also to be emphasized that many salivas came from individuals in poor health (carcinoma or ulcer ventriculi, ulcer duodeni, cachexia from liver, gall-tract or gastric secretory malfunction, and the like). We have not been able to find in the literature a satisfactory discussion of the influence of disease on reaction or chemical properties of saliva. The observation we present is certainly interesting and perhaps not altogether unimportant. Of twenty salivas from healthy young adults seventeen (85 per cent.) were neutral in reaction. The time following the ingestion of food in the test-meal cases during which saliva was collected may also have some bearing on its reaction.

TABLE 2.—THE PEPTID-SPLITTING POWER OF CENTRIFUGALIZED SALIVA

No. of Cases.	Positive Reactions*			Neg. Reactions.	Tryptophan Test.	Reaction of Saliva.	Percentage.
	+	++	+++				
92	39	20	14	19	0	Neutral	Pos. 78.9 Neg. 21 +
106	44	40	7	15	1	Acid	Pos. 85.8 Neg. 14.1 +
6	2	1	0	3	0	Alkaline	Pos. 50 Neg. 50
204	85	61	21	37	1		

*Degree of reaction: Lilac = +; rose-pink = ++; rose-purple = +++.

Total Pos. (all degrees) = 167 or 81.8+ per cent.

Total Neg. (all degrees) = 37 or 18.1+ per cent.

4. *Consideration of Oral Conditions on the Peptid-Splitting Power of Saliva.*—(a) *Teeth*: Notes were made relative to the condition of the donor's teeth at the time that saliva was received from him. The classification in Table 3 needs little explanation. In practically all instances in which teeth were called "poor" or "very poor," there was pyorrhea in addition to dirty, decaying teeth. Some teeth classed as "good" or "fair" also showed pyorrhea. In these and other instances frequently diseased tonsils or foul nasopharyngeal discharge were not lacking.

The interesting features of Table 3 are the following: Of the 334 salivas tested, approximately but one-fourth of the number came from subjects with good teeth, while more than one-half of the specimens were received from individuals with inferior and dirty teeth. From the latter class we never received a saliva incapable of splitting glycyltryptophan, while from 12.5 per cent. of salivas from the good teeth class, the cleavage property of saliva for the dipeptid was not demonstrated. The differences in degree of reaction are striking. In the good teeth class, the majority of the reactions are in grades + or +- , while in the very poor teeth

groups the preponderance of the reactions fall in grades ++ and ++++. Twenty-six (7.5 per cent.) of the salivas in our series came from individuals with artificial teeth. Of this number 15. + per cent. of the salivas did not split glycytryptophan. These were from clean mouths in three instances and from a dirty mouth in a fourth. In this group (artificial teeth), thirteen (50 per cent.) of the salivas showed very strong cleavage power. In the majority of these, both artificial teeth and patients' mouths were very dirty.

TABLE 3.—THE RELATION OF THE CONDITION OF THE TEETH TO PEPTID-SPLITTING POWER OF SALIVA

No. of Specimens.	Teeth—State	Reaction *			
		0	+	++	+++
84	Good	10	35	27	12
50	Fair	6	13	17	14
88	Poor	0	18	28	42
86	Very poor	0	21	18	47
26	Artificial	4	4	5	13

*Degree of reaction: Lilac = +; rose-pink = ++; rose-purple = +++.

(b) *Gums*: Of 334 individuals, 201 (60. + per cent.) showed erosions at the teeth-gum margins, or definite pyorrhea alveolaris. Of this number, the saliva was acid in 149 instances (74.1 per cent.). These specimens split glycytryptophan in 189 instances (94.3 per cent.).

(c) *Tonsils and Nasopharynx*: Salivas were collected from 192 persons in which these parts were inspected. In fifty-three instances (27.5 per cent.) there was evidence of tonsillar disease (enlargements, crypts, exudate, erosion). In thirty-eight instances (19.7 per cent.) there were evidences of nasopharyngeal inflammation. In six instances (3.1 per cent.) there were ulcerative conditions of the oral mucosa, apart from adenoid hypertrophy or pyorrhea.

Of the 192 individuals whose tonsils, oral mucosa, etc., were examined, seventy-three (38. + per cent.) revealed some abnormality. Of this number forty-two (57.5 per cent.) had acid salivas and thirty-one (42.4 per cent.) of these salivas split glycytryptophan after incubation for twenty-four hours at 37 C.

(d) *The Use of Tobacco*: Of the 334 specimens of saliva examined 209 came from males. In 110 instances data were obtained regarding the use of tobacco. Seventy-eight smoked or chewed tobacco, or both. Three of these also used snuff. Saliva from these seventy-eight individuals split glycytryptophan in sixty-nine instances (89.8 per cent.), irrespective of its reaction to litmus. Twenty-five donors chewed tobacco, but did not smoke regularly. Eleven of these had acid salivas. Twenty-two "chewers" donated salivas which split glycytryptophan in fifteen instances (68.1 per cent.).

(c) *The Effect of Mouth-Washes:* A water solution of alphozone of 0.4 per cent. strength was used vigorously as a mouth- and teeth-wash in fifty-two instances. The subjects were directed to hold the solution in their mouths for several minutes, to force it back and forth between their teeth and about the alveolar spaces, and to gargle a portion. The mouth was then rinsed with warm normal salt solution. Saliva was then collected for forty-five minutes. From the fifty-two donors saliva was alkaline or neutral in thirty-eight instances (73 per cent.) and acid in fourteen instances (26.9 per cent.). From this group of fifty-two specimens, cleavage of glycytryptophan occurred but seventeen times (32.7 per cent.). With respect to degree of cleavage, the reaction was in no instance beyond $++$.

The results obtained after the use of the strong alphozone solution as a mouth-wash led us to test the effects of it and like solutions on saliva directly, and to experiment with mouth and throat cultures of bacteria.

5. *Consideration of the Effect of Temperature on the Peptid-Splitting Power of Saliva.—Boiling:* A portion of saliva from each of 302 specimens combining all reactions was immersed in a plugged sterile test-tube in water and kept boiling for thirty minutes, glycytryptophan solution was added after the saliva had been cooled, and the mixture was then placed under toluol in the thermostat for twenty-four hours. Test for tryptophan was then made in the usual manner. In none of the boiled specimens could free amino-acid be detected.

Room Temperature: Portions of 160 specimens of saliva were mixed with glycytryptophan and left under toluol for from twelve to 120 hours, at room temperature (about 75 to 80 F.). Table 4 summarizes the result.

TABLE 4.—THE CLEAVAGE POWER OF SALIVA AT ROOM TEMPERATURE

No. of Specimens.	Reaction.	+ Reaction (Cleavage) after Hours:								No. of Specimens Showing No Cleavage.
		12	24	36	48	72	96	120		
66	Acid	3	7	29	16	5	4	0	2	
82	Neutral	6	30	26	7	9	0	0	4	
12	Alkaline	2	8	0	1	0	0	0	1	
<hr/>		<hr/>								
160		11	45	55	24	14	4	0	7	

Briefly, it is seen that irrespective of the reaction of saliva, cleavage of the dipeptid occurs in the majority of instances between twenty-four and thirty-six hours after admixture; that in a few instances cleavage may have taken place within twelve hours or may be delayed ninety-six hours, or no free amino-acid may be detected at the end of 120 hours (seven instances); that neutral and alkaline salivas split glycytryptophan somewhat more rapidly than do acid salivas at room temperature.

Ice-Box Temperature: Thirty-five specimens of whole saliva of the several reactions were mixed with glycyltryptophan under toluol and kept on ice. Portions tested within twenty-four to 522 hours showed in no instance hydrolyzation of the dipeptid. Of these thirty-five specimens, after being on ice over 522 hours, twenty-nine were placed in the thermostat at 37 C., and twenty-six showed free tryptophan after eighteen hours.

Graded Temperatures: Specimens of saliva were variously heated in plugged sterile test-tubes, cooled in running water, combined with glycyltryptophan solution and placed in a thermostat under toluol for twenty-four hours. This mixture, acidulated, was then tested for free amino-acid. Table 5 shows the results.

TABLE 5.—THE INFLUENCE OF GRADED TEMPERATURES ON THE PEPTID-SPLITTING POWER OF SALIVA

No. of Specimens	Reaction of Saliva	Reactions at Temperature:												
		20 C.	30 C.	40 C.	45 C.	50 C.	55 C.	60 C.	65 C.	70 C.	75 C.	80 C.	90 C.	100 C.
28	Acid....	25	22	26	23	23	21	22	14	8	1	0	0	0
34	Neutral..	33	31	29	30	26	26	24	22	21	3	0	0	0
9	Alkaline.	9	9	8	7	6	7	5	5	5	0	0	0	0
71		67	62	63	60	55	54	51	41	34	4	0	0	0

It is seen that, irrespective of the reaction of the saliva, of seventy-one specimens examined, there is uniform cleavage up to 60 C. Between 60 and 75 C., there is rapid diminution in peptid-splitting power, varying with reaction somewhat (neutral saliva being most resistant to increased heat). We never had any specimen show cleavage of glycyltryptophan after it had been heated above 75 C. The variations in splitting power of the specimens with different reactions would appear to be somewhat dependent on such reaction, although there may be other factors (thick, clumpy, or dirty saliva).

6. *Effect of Chemical Solutions on the Peptid-Splitting Power of Saliva:* In these experiments the following solutions were used:

1. Phenol (carbolic acid) in water, 2 per cent.
2. Bichlorid of mereury in water, 1 per cent.
3. Alphozone in water, 0.1 per cent., 0.2 per cent., 0.3 per cent., 0.4 per cent.
4. Antiformin (commercial solution).
5. Absolute alcohol.
6. Acetic acid, glacial.
7. Chloroform.
8. Ferric chlorid solution, 5 per cent.

Procedure.—After specimens of saliva had been tested for free amino-acid and found negative, equal portions were respectively combined with glycyltryptophan solution plus 1 c.c. of the solution of the chemical com-

bination under consideration. Controls of portions of saliva without glycytryptophan solution and also of the glycytryptophan solution itself were set up. The tubes were then incubated under toluol for twenty-four hours, when they were made acid (if not already acid) with 3 per cent. acetic acid solution and tested for free tryptophan in the usual manner. Table 6 shows the experiments and results in detail.

TABLE 6.—THE INFLUENCE OF CHEMICAL ACTION ON PEPTID-SPLITTING POWER OF SALIVA

No. of Series	No. of Specimens	Combination Tested	No. of Positives	No. of Negatives	Controls					
					Glycytryp- tophan + Saliva		Glycytryp- tophan alone		Saliva alone	
					Pos.	Neg.	Pos.	Neg.	Pos.	Neg.
1	25	2% phenol + saliva and glycytryptophan	0	25	23	2	0	25	0	25
2	25	1% mercuric chlorid + saliva + glycy- tryptophan	0	25	25	0	0	25	0	25
3	25	Antiformin + saliva + glycytryptophan	0	25	21	4	0	25	0	25
4	25	Glacial acetic acid + saliva + glycytryp- tophan	0	25	23	2	0	25	1	24
5	25	Chloroform + saliva + glycytryptophan	0	25	24	1	0	25	0	25
6	25	5% ferric chlorid + saliva + glycytryp- tophan	3	22	24	1	0	25	0	25
7	80	Absolute alcohol + saliva + glycytryp- tophan	0	80	74	6	0	80	0	80
8	50	0.1% alphozone + saliva + glycytryp- tophan	32	18	46	4	0	50	0	50
	50	0.2% alphozone + saliva + glycytryp- tophan	24	26	46	4	0	50	0	50
	50	0.3% alphozone + saliva + glycytryp- tophan	11	39	46	4	0	50	0	50
	50	0.4% alphozone + saliva + glycytryp- tophan	0	50	46	4	0	50	0	50

It will be observed that solutions of 2 per cent. phenol, 1 per cent. HgCl_2 , antiformin, glacial acetic acid, chloroform and absolute alcohol and 0.4 per cent. alphozone absolutely inhibit the peptid-splitting agent in human saliva. A 5 per cent. solution of ferric chlorid prevented cleavage in 88 per cent. of specimens.

Brief attention may be called to the action of the alphozone solutions. After we had conducted the experiments on salivas from individuals who had used alphozone solution as a mouth-wash, we carried out a few tests (not included in the series of Table 6) in which we used a 0.1 per cent. solution of alphozone combined with saliva. We found that several of

the thick tenacious or dirty salivas retained good cleavage power for glycytryptophan even after so powerful an organic peroxid as alphozone had been added. When the experiments for Table 6 were set up, various strengths of alphozone were added in the attempt to discover the limit at which cleavage of the dipeptid was possible with this admixture. It is seen by Table 6 that only solutions so powerful as 0.4 per cent. alphozone uniformly inhibit the peptid-splitting power of whole saliva and that diminution in strength of solution results in proportionate increase in the number of salivas which retain that power.

With exception of the alphozone and chloroform additions to saliva-glycytryptophan mixtures in our series there were always various grades of precipitation in the combinations when the numerous test solutions were added. It would seem that this fact might seriously interfere with the action of the peptid cleaving agent in saliva, if that agent be an enzyme. Precipitation may not, however, be the only factor. Chloroform and alphozone admixtures produce no marked precipitation in saliva-glycytryptophan solutions. Chloroform absolutely inhibited cleavage in our experiments. Alphozone solutions only inhibited cleavage of the dipeptid above 0.3 per cent. strength. In addition to the question of increase in alkalinity in alphozone-saliva mixtures, as the percentage of alphozone increases in such solutions one must also consider the importance of alphozone as a germicide. Inasmuch as in our experiments alphozone was the only chemical agent added to saliva, which did not cause precipitation of protein, and yet did not invariably inhibit cleavage, its results only can be used to indicate a line of demarcation respecting a factor, at least, in explanation of how saliva splits glycytryptophan. It is well known that chemicals that precipitate protein in enzyme-containing solutions, also inhibit the ferment action of those solutions. Inhibition of the peptid-splitting agent in saliva by such chemical solutions as phenol, mercuric chlorid, antiformin, alcohol and the like, leaves us in doubt as to whether or not such agent was rendered inert by precipitation of an enzyme with protein in saliva or cleavage power was lost by bactericidal action of these strong germicides, or both. Ferric chlorid solutions which precipitate protein in saliva are not very strongly germicidal, apart from mechanical action. In 88 per cent. of specimens cleavage of glycytryptophan was inhibited by 5 per cent. ferric chlorid solution.

7. Effect of Bacteria on Cleavage of Glycytryptophan:

A. *Saliva + Bacteria.*—Cultures from twenty-seven specimens of saliva were made in (a) bouillon, on (b) nutrient agar and on (c) blood-serum-agar. These were allowed to remain three days in the water bath at 37 C. In reaction the salivas from which cultures were made were alkaline, three; neutral, fifteen, and acid, 9.

Table 7 gives details regarding salivas, organisms returned by cultures, etc. At the end of the incubation period, experiments were set up as follows:

TABLE 7.—EFFECT OF BACTERIA ON CLEAVAGE OF GLYCYLTRYPTOPHAN

Series No.	Patient's Number	Reaction of Saliva	Teeth	Organisms in Cultures	Results				Remarks
					Series a Pos.	Series a Neg.	Series b Pos.	Series b Neg.	
1	47285	Alkaline	Good	Streptococci, staphylococci, diplococci, short bacilli.	+	0	0	+	
2	67218	Alkaline	Good	Cocci, lance-shaped bacilli.	0	+	0	+	Adenoids.
3	67232	Alkaline	False	Cocci, diplococci, spirillæ.	++	0	0	+	
4	66886	Neutral	False	Diplococci, streptococci, short rods.	+	0	0	+	
5	9596	Neutral	Good	Cocci and short bacilli	Tr	0	0	+	Pyorrhea.
6	67244	Neutral	Fair	Cocci, rods and spirillæ.	Tr	0	0	+	
7	67292	Neutral	Good	Staphylococci and streptococci, lance-shaped bacilli.	+	0	0	+	Diseased tonsils.
8	67285	Neutral	Poor	Cercomonas in fresh specimen, cocci, spirillæ and rods.	++	0	0	+	Pyorrhea ++
9	67328	Neutral	Good	Diplobacilli, diplococci, staphylococci.	0	+	0	+	Pyorrhea.
10	67352	Neutral	Good	Streptococci and staphylococci, few bacilli.	+	0	0	+	
11	67338	Neutral	Fair	Micrococcus, streptococci, staphylococci.	+	0	0	+	Dirty teeth.
12	67368	Neutral	Good	Cocci, lance-shaped bacilli.	?	0	0	+	
13	67336	Neutral	Good	Short rods, cocci, spirillæ.	+	0	0	+	Pyorrhea +
14	67342	Neutral	Fair	Cocci, diplobacilli, leptothrix.	Tr	0	0	+	Large tonsils.
15	67313	Neutral	Good	Micrococci, streptococci, staphylococci, short bacilli.	+	0	0	+	
16	28954	Neutral	Poor	Spirillæ in fresh bacilli, diplococci, and streptococci.	++	0	0	+	Many carious teeth.
17	67404	Neutral	Fair	Bacilli and cocci	+	0	0	+	Several cavities, pyorrhea.
18	67365	Neutral	Good	Staphylococci, diplobacilli.	Tr	0	0	+	
19	67206	Acid	Poor	Diplococcus, strepto- and staphylococci, bacilli.	++	0	0	+	Cavities in teeth.
20	67213	Acid	Good	Streptococci, staphylococci, lance-shaped rods.	Tr	0	0	+	
21	51204	Acid	Fair	Micrococci, streptococci, rods.	+	0	0	+	
22	67295	Acid	Fair	Staphylococci, streptococci, diplobacilli	+	0	0	+	
23	57318	Acid	Poor	Streptococci, staphylococci, bacilli, spirillæ.	++	0	0	+	Carious teeth.
24	67332	Acid	Very Poor	Staphylococci, streptococci, short bacilli, diplococci, leptothrix.	+	0	0	+	Many stumps, and teeth with cavities.
25	67268	Acid	Good	Cocci, diplobacilli.	Tr	0	0	+	
26	67431	Acid	Good	Cocci, diplobacilli	Tr	0	0	+	
27	67371	Acid	False	Cocci, short and long rods.	0	+	0	+	

Portions of salivas collected during the three days that the cultures were growing and which had been shown to be capable of splitting glycytryptophan, were heated at 100 C. in a water bath for one hour. The specimens were then cooled in running water and made neutral with N/10 sodium carbonate. Two series were then made from the specimen. (a) Saliva + glycytryptophan solution + emulsions of bacteria from each set of cultures from saliva. (b) Saliva + glycytryptophan + toluol. (Controls.) The sets were then thoroughly mixed and incubated forty hours at 37 C. Portions of mixtures were then acidulated and tested in the usual way for free tryptophan. Table 7 shows the results.

It is seen that twenty-three out of twenty-seven salivas which had been rendered incapable of splitting glycytryptophan by heating to 100 C. are capable of showing some evidences of cleavage power after being mixed with bacteria grown from specimens of saliva. In none of the controls was cleavage power exhibited. In sixteen out of the twenty-seven sets, free tryptophan was readily recognized on the addition of bromin vapor. In seven instances there was but a trace of free tryptophan. In one instance the result was questionable. In three experiments (11.1 + per cent.) no free tryptophan could be detected. The reaction of salivas from which cultures were made appeared to have no great bearing on the results. Very rich flora in such salivas appeared to determine largely the degree of reaction. Rich flora were frequently present from salivas whose donors had very poor teeth or marked pyorrhea, but this was not constant. Nasopharyngeal conditions appeared to have bearing on quantity and variety of bacteria present in salivas.

Except as in Table 7, we have made no attempt to determine the exact organisms appearing to have some influence on cleavage of glycytryptophan, apart from noting the groups returned by cultures from each of the twenty-seven specimens of saliva examined. It would seem from the considerations of these groups that symbiosis of the organisms appeared to be responsible for certain creptic power on glycytryptophan.

B. Direct Effect of Cultures of Bacteria from Saliva Upon Glycytryptophan.—Transplants from the cultures from the twenty-seven specimens of saliva mentioned above (A) were made on fifty-four tubes of nutrient agar. These were incubated at 37 C. for forty-eight hours. Growths resulted in all instances, the organisms being streptococci, staphylococci, micrococci, bacilli of varying lengths, diplococci and a few leptothrix.

To one-half (twenty-seven) of the tubes was then added 0.5 c.c. glycytryptophan solution in 5 c.c. warm normal salt solution. To the remaining tubes 5 c.c. normal saline solution alone were added. The tubes were incubated thirty-six hours. At the end of incubation, the fluid from each tube was drawn off and after acidulation each specimen was tested for free tryptophan by bromin vapor. Table 7 gives details regarding the organisms.

Result.—In none of the fluids from culture tubes to which normal salt solution alone had been added was free tryptophan shown. Twenty-one (77.7 + per cent.) of the twenty-seven fluids from cultures where the glycytryptophan-salt solution had been added showed free tryptophan. The color changes ranged from pale lilac to rich rose pink.

SUMMARY

From the work outlined in this report the following seems apparent:

1. Reaction appears to have little bearing on power of saliva to split glycytryptophan.

2. Free tryptophan is occasionally met with in salivas from dirty or infected oral cavities.

3. Centrifugalization of saliva lessens its power to cleave glycytryptophan. This is rather more marked in alkaline or neutral salivas.

4. Conditions of health and state of oral cavities of donors seem to affect reaction of saliva, with some apparent influence on the peptid hydrolyzing power of such saliva.

5. Power to hydrolyze glycytryptophan is lost when saliva is heated above 75 C. The optimum temperature for cleavage is about 37 C. At ice-box temperature cleavage is not carried on, but specimens kept at such temperature for as long as 522 hours, may hydrolyze the dipeptid when incubated subsequently at 37 C. At room temperature, cleavage is delayed, but is nevertheless carried on, apparently irrespective of the reaction of saliva.

6. The chewing of tobacco seems to lessen the power of certain salivas to hydrolyze glycytryptophan. Smoking of tobacco appears to have little effect.

7. The use of strong mouth-washes (e. g., an organic peroxid, as alphozone) results in marked diminution of peptid-splitting power of certain salivas.

8. Strong chemical action on saliva, particularly when the addition of such chemicals causes precipitation of protein, inhibits its glycytryptophan splitting power. Many such chemical solutions tested in this report were germicides.

Non-protein precipitating germicides (as the organic peroxid group) inhibit the peptid-splitting power of saliva roughly in direct proportion to strength of such solutions.

9. Cultures of bacteria grown from salivas, may, after salivas have lost their power to split glycytryptophan (by heating to 100 C.) cause such salivas to split that dipeptid by admixture with salivas and subsequent incubation.

10. Solutions of glycytryptophan added directly to cultures of bacteria grown from saliva are readily split with liberation of free tryptophan.

11. The indefinite nature of any enzyme renders its actual demonstration difficult. While the agent in saliva causing cleavage of the dipeptid glycytryptophan has certain characteristics of an enzyme, it would seem that a not inconsiderable factor in such cleavage power is the action of normal or pathologic oral microorganisms, or products of their growth.

A CONTRIBUTION TO THE SYMPTOMATOLOGY OF THROMBOPHLEBITIS IN TYPHOID *

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Everyone who sees any considerable number of typhoid fever cases, year after year must have been struck with the fact that, while most of these run a fairly typical and uneventful course, there is a very considerable group of cases in which the latter part of the course, or the period of convalescence, is marked by a number of obscure and apparently unrelated symptoms and complications. If one takes the trouble to read over a large number of case histories and charts of typhoid this fact is brought out even more clearly and forcibly: for many of these incidents are so transient and apparently insignificant that they fail to make much impression and are readily forgotten.

These symptoms include various forms of irregular febrile movement; sudden pulmonary and pleural symptoms; sudden and unaccountable abdominal symptoms; repeated chills, without obvious cause; pain, discomfort and stiffness in the legs or arms; pain in the heel; tenderness of the toes, etc. In some, but by no means in all, of these cases, frank signs of thrombophlebitis¹ appear at some time in the course of the illness.

It is my purpose in the present paper to attempt to show that many or most of these obscure late interruptions of the normal course of typhoid have a common underlying cause and that this cause is thrombophlebitis.

Before considering the individual symptoms it will be necessary to call attention to certain facts concerning phlebitis itself as it is seen in typhoid fever.

Thrombophlebitis probably a much more frequent complication than is commonly supposed: In most writings on the subject the incidence of this complication of typhoid is placed at about 2 per cent. In 829 cases studied by Osler² the percentage was 1.9. In Thayer's analysis³ of 1,463

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¹From the Medical Service of the New York Hospital.

1. In the present article the terms thrombosis and phlebitis are used interchangeably and without distinction to denote the whole process included in the longer term thrombophlebitis, and no attempt is made to settle the still uncertain and much discussed question as to whether the formation of the thrombus or the inflammation of the vein wall is the primary process. The weight of evidence at present, however, seems to favor the view that thrombosis occurs first.

2. Osler: *Studies in Typhoid Fever*. Johns Hopkins Hosp. Rep., viii, p. 458 et seq.

cases venous thrombosis occurred in 2.6 per cent. My own belief is that these figures do not begin to represent the actual frequency of this complication. Among 1,540 cases of typhoid treated in the New York Hospital between 1898 and 1912 there were seventy-eight instances of undoubted venous thrombosis (5 per cent.). If to this number be added the cases in which no thrombosis was recognized but which presented other symptoms that, as I hope to show, are usually indicative of the existence of a latent thrombosis, the percentage is increased to 8 or 9. Da Costa⁴ reports that, in a series of 135 soldiers treated for typhoid in the Pennsylvania Hospital during the Spanish American war, the complication of milk-leg occurred sixteen times, or in nearly 12 per cent. Vincent,⁵ in a group of cases studied by him, found the complication of phlebitis in 8.23 per cent.

It is my conviction that the further study of this complication in its various phases, and especially the more prompt recognition of its milder and less characteristic manifestations, will show that venous thrombosis occurs in from 10 to 15 per cent. of all cases of typhoid fever.

The development of thrombophlebitis is gradual, and its classical symptoms appear only late in the process: The recent beautiful histological studies of Aschoff⁶ show that the formation of the primary white thrombus is due to the gradual deposit, layer on layer, of blood platelets, while the blood is still flowing in the affected vein, in a manner somewhat comparable to the formation of a bar by the gradual deposit of slit in a flowing stream. The complete occlusion of the vein is a late phase of this process. The symptoms by which thrombophlebitis is ordinarily recognized—edema, pain, tenderness and periphlebitic induration—are seen usually only after such occlusion has occurred, for not until then do the signs of inflammation of the vein wall, and especially of the surrounding tissue, become pronounced. Up to that time the process of thrombosis either runs a latent course or manifests itself by symptoms so mild or so little characteristic that they are apt to be overlooked or misunderstood.

Vaquez,⁷ in his admirable study of phlebitis, lays stress on the fact that this process need not result in complete occlusion of the lumen of the vein, and adds that "to wait until there is a total obliteration before saying that, clinically and anatomically, there is a phlegmasia alba dolens

3. Thayer: An Analysis of 42 Cases of Venous Thrombosis Occurring in the Course of Typhoid Fever. *Med. News*, 1904, lxxxv, 637.

4. Da Costa: An Unusual Percentage of Cases of Milk Leg Following Typhoid Fever. *Internat. Med. Mag.*, 1899, viii, 4.

5. Vincent: Bactériologie des phlébites dans la fièvre typhoïde. *Semaine méd.*, 1895, xv, 377.

6. Aschoff, et al: Beiträge zur Thrombosefrage. Leipzig, 1912.

7. Vaquez: De la phlébite. *Clin. méd. de la Charité*, 1894, p. 751.

is an error analagous to that made by waiting for the existence of pulmonary cavities in order to diagnosticate tuberculosis."

That extensive thrombosis of the veins of the extremities may develop without giving recognizable symptoms has often been demonstrated by the post mortem examination of patients dying of pulmonary embolism. The obstetrical, gynecological and surgical literatures abound with such instances. Vaquez,⁷ in discussing the phlegmasia alba dolens which declares itself during the convalescence of typhoid, insists that the process itself often begins insidiously and latently long before the symptoms appear. In support of this statement it would be easy to cite many instances from among the typhoid cases included in this study, if space permitted.

The thrombotic process in typhoid tends to be much more extensive and widely disseminated than the symptoms would seem to indicate: One of the points brought out clearly in the present study is that the thrombosis is usually widely scattered and extensive even when the frank symptoms of the trouble may be quite circumscribed. For example, there may be slight pain, or muscular soreness, or points of tenderness in both calves and feet and then, some days or weeks later, distinct signs of phlebitis—i. e., marked tenderness and periphlebitic induration—only over a small area of one femoral vein. In other cases there will be frank signs of phlebitis only in one leg or thigh, and yet, some weeks later, after patient has been permitted to get up, there will be marked edema of *both* legs. Not so very infrequently, in addition to phlebitis of the leg veins, there will be pain and more or less tenderness of one or the other arm. In one woman there was, in addition to phlebitis in both legs, distinct involvement of the veins of first one and then the other breast. Occasionally the process will seem to be confined chiefly to the small, superficial veins and will show a tendency to migrate from spot to spot over the legs, buttocks and lower part of the trunk.

THE PULMONARY COMPLICATIONS OF THROMBOPHLEBITIS

Although it is well known that pulmonary embolism is an occasional complication of venous thrombosis, attention has been centered chiefly on the large, fatal emboli which, while fortunately rare, are yet so dramatic in their occurrence and so tragic in their results as to leave a deep impression when they do occur. Such emboli usually result from the separation of a fragment from a thrombus occupying, and occluding, some large vein such as the femoral or iliac. They therefore are apt to occur late in the course of the phlebitic process. But there is another and much commoner type of pulmonary embolism which differs radically from that just

referred to in its time of occurrence, clinical course and prognosis, and which has received far less attention than it deserves.

As a result of some personal experiences with this latter type I published recently a short paper⁸ calling attention to the comparatively frequent appearance of small pulmonary emboli in the course of venous thrombosis and especially to the fact that such emboli in many cases make their appearance a number of days, or even two or three weeks, before any signs of thrombophlebitis can be detected. In seven of the nine cases reported the thrombosis had occurred in the course of typhoid fever. It seemed to me, therefore, that it might be instructive to go over the records of a large number of cases of typhoid with a view to ascertaining, first, what proportion of these cases complicated by phlebitis showed evidences of such pulmonary embolism, and, second, what proportion of the pulmonary and pleural complications of typhoid could reasonably be ascribed to pulmonary embolism and infarction. With these points in mind the records of all cases of typhoid treated in the New York Hospital between 1898 and 1912 in which the complications of phlebitis, pneumonia or pleurisy were recognized have been carefully analysed, and the results of this analysis form the basis of this paper.

Among the 1,540 cases of typhoid there were eighty-eight with pulmonary or pleural complications, exclusive of bronchitis. Among the eighty-eight cases there were twenty-five (28 per cent.) in which the thoracic complications were almost certainly *not* of embolic nature. (These twenty-five cases formed a group having a strikingly uniform and sharply defined clinical picture. Almost without exception the pulmonary symptoms appeared early in the disease and began as a severe general bronchitis. This grew progressively worse and sooner or later resulted in bronchopneumonia, which was usually double and which usually involved the greater part of both lower lobes. Seventeen of these cases terminated fatally.)

There were eight cases (9 per cent.) complicated by phlebitis which showed, at some time, pulmonary symptoms, but these symptoms were either not sufficiently characteristic or the records not sufficiently complete to warrant their being included among the cases of pulmonary embolism. Some of these cases, however, were almost certainly of this nature.

There were, further, twenty-six cases (30 per cent.) in which the character of the thoracic symptoms made it seem very probable indeed that they were instances of pulmonary embolism but in which the records furnished no other evidence of thrombophlebitis. Finally there were twenty-nine cases (33 per cent.) in which there were frank signs of

8. Conner, L. A.: Pulmonary Symptoms as Premonitory Signs of Venous Thrombosis. Med. Rec., New York, April 29, 1911

phlebitis and in which the pulmonary or pleural symptoms could be assumed with reasonable certainty to be due to embolism and infarction.

Among these twenty-nine cases of pulmonary embolism nineteen gave their symptoms of this condition before the phlebitis had declared itself and ten after the signs of phlebitis had appeared.

The above figures may be tabulated thus:

	Cases	Per cent.
Pulmonary and pleural complications (exclusive of bronchitis)	88	
Pulmonary embolism before appearance of phlebitis 19	29	33
Pulmonary embolism after appearance of phlebitis 10		
Phlebitis with pulmonary symptoms of doubtful nature	8	9
Probable pulmonary embolism without evident phlebitis	26	30
Pulmonary complications not embolic	25	28

The evidence on which is based the conclusion that a very large proportion of the pulmonary and pleural complications of typhoid are embolic in nature is and necessarily must be chiefly circumstantial. Such emboli are almost always small; the patients rarely die, and none of our cases has come to autopsy. Since the evidence is largely circumstantial its force depends on the accumulation and massing of it. It has therefore seemed to me necessary to record, in condensed form, all of the case histories. Whoever has the patience to read through these, case after case, will be likely to recognize a fairly distinct clinical picture, and in reading the cases of probable embolism without evident phlebitis will be convinced, I believe, that most of them are really cases of embolism.

The character of the records of the medical service of the New York Hospital probably does not differ materially from that of records of other hospitals of the same class. They have the failings inherent in a system which places chiefly on the, often overworked, intern staff the responsibility for the proper recording of the progress of the patients and of most of the daily events of the wards. These failings are usually chiefly sins of omission. Many transient and apparently unimportant symptoms, which may have been promptly recognized and properly cared for, are yet not noted in the permanent records of the patient. It is reasonable to assume, therefore, that the records of the cases under consideration sometimes fail to include facts that might have served to identify a mild phlebitis or a small pulmonary embolism and that the figures as given above, if they err at all, do so on the side of conservatism.

SYMPTOMS OF PULMONARY EMBOLISM AS SEEN IN TYPHOID FEVER

As has been said already there are two quite distinct types of pulmonary embolism. In one the embolus is large; the attack is violent and usually fatal, and the symptoms, as a rule, appear only late in the course of the phlebitis. In the other the embolus is small, the symptoms are often very mild and transient, the prognosis is good and the attack, in a majority of the cases, occurs some days before any of the usual symp-

toms of phlebitis can be discovered. The first type is rare; the second is relatively common. In the latter type the character of the symptoms and the time of their occurrence make it highly probable that these small emboli are derived from the freshly forming and friable mural thrombus before it has occluded the vein and while the blood is still flowing past it. That is the time when the thrombosis usually gives no local symptoms and the time also when one would naturally expect small particles to be carried away into the venous blood stream. Indeed, it is difficult to conceive of the gradual formation of a thrombus, by the deposit of blood platelets on the wall of a still patent vein, without some fragments being washed away and ultimately deposited in the lung capillaries; and one is inclined to wonder, not at the frequency of embolism in the early stages of thrombosis, but rather that a case of thrombosis should ever run its course without such early pulmonary emboli.

The observation that phlebitis may give rise to pulmonary embolism long before it manifests itself by local symptoms is by no means a new one. Vaquez,⁷ in describing various modes of onset of phlebitis, speaks of one under the caption "*Phlébite latente à début embolique.*" Such patients, in the course of some affection likely to be associated with phlebitis, "suddenly feel a stitch in the side followed by a little fever, sometimes with some bloody sputa. The trouble, which may be ascribed to an intercostal neuralgia or to a slight focus of congestion, rapidly disappears; then sometimes the same phenomena are repeated two or three times. Finally eight, ten or fifteen days afterward a phlebitis suddenly appears in one of the extremities."

Vialard⁹ reports four examples of early pulmonary infarction in phlegmasia alba dolens. A number of such instances can be found also among the cases reported by Mahler¹⁰ and by Zurhelle.¹¹

A study of the cases cited by Osler² in his exhaustive "Studies in Typhoid Fever" shows this same association of obscure pulmonary and pleural symptoms with phlebitis. For example, Case 13,813 is cited among the cases complicated by pneumonia and also among those complicated by phlebitis. Cases 17,319 and 18,156 are mentioned under the heading of the complication of pleurisy and under that of phlebitis. Case 13,524 appears under the three groupings of "painful legs," pleurisy, and post-typhoid elevation of temperature.

An analysis of the twenty-nine cases of pulmonary embolism occurring with known phlebitis shows that *thoracic pain* was present at some

9. Vialard: Des embolies pulmonaires préphlébitiques pendant les suites de couchés. Jour. de méd. et de chir., 1904, lxxv, 62.

10. Mahler: Thrombose, Lungenembolie und plötzlicher Tod. Arbeit. a. d. koenigl. Frauenklinik in Dresden, 1895, ii, 72.

11. Zurhelle: Thrombose und Embolie nach gynäkologischen Operationen. Arch. f. gynäk., 1907, lxxxiv, 443.

time in almost every case. In a majority of the cases it was the first symptom noticed. The pain was usually sudden, sharp and severe and was felt commonly in the lower part of one or the other axilla. Occasionally it was referred to the hypogastrium, the shoulder or the lower part of the neck. The duration of the pain varied from a few hours to a number of days. *Cough* was present in most but not in all cases. In eight instances it was the first symptom. Sometimes it did not appear until two or three days after the onset of the pain.

Bloody sputum was noted in thirteen (45 per cent.) of the cases. It sometimes appeared promptly, but frequently was seen only several days after the onset of the attack. Often the blood-spitting continued for many days. The blood was raised usually in small clots or streaks. At the onset such sputa are usually bright red; they soon become dark, however, and, if the spitting continues for many days, the altered blood gives a brownish color to the sputum. True rusty sputum was never seen.

Sudden thoracic oppression and dyspnea were present at the onset of the attack in only three cases. In five instances the pulmonary attack was introduced by one or more *chills*.

The behavior of the *temperature* varied much. In some cases it rose abruptly with the advent of the thoracic symptoms, but often it was not easy to determine whether the variations in the temperature were to be ascribed to the phlebitis, to the embolism or to the primary disease.

Rigidity of the upper portion of the abdominal musculature, and tenderness just below the ribs were present in several cases in which the infarction seemed to be situated at the diaphragmatic surface of the lung.

Multiple Embolism: In thirteen of the twenty-nine cases the symptoms were such as to indicate the occurrence of two or more attacks of pulmonary embolism. Among the cases of probable embolism without signs of phlebitis there were five in which the multiple character of the pulmonary attacks leaves little room for doubt as to their true nature. In one of these (Case 39) there were four distinct attacks during a period of three and a half weeks.

Fatal Embolism: Death occurred in three of the twenty-nine cases of pulmonary embolism with recognizable phlebitis (Cases 22, 27, 28). In each instance the fatal attack occurred late in the course of the phlebitis and had been preceded by milder pulmonary attacks.

Physical Signs: As regards their physical signs the cases may be divided into three groups:

1. Those in which friction rubs or crepitant râles over a small area were the only signs. These signs often lasted only two or three days.
2. Cases in which the signs were those of a small, circumscribed pneumonia. The area of consolidation did not extend and in each

instance the signs of consolidation disappeared within three or four days. These signs were almost always in the lower lobes.

3. Cases with signs of extensive plastic pleurisy or of pleural effusion. This type included more than half of all the cases. In some of these the physical signs at first were those of consolidation. It seemed to be quite characteristic of the third group of cases that although the signs seemed to indicate the presence of liquid, exploratory puncture usually failed to reveal it. In only three cases was serum obtained and in only one of these was there any considerable quantity.

CASE REPORTS

PULMONARY EMBOLISM BEFORE THE APPEARANCE OF SIGNS OF THROMBOPHLEBITIS

CASE 1.—D. R. D., male, aged 32. No. 1373. Admitted October 23, 1898, on ninth (?) day of illness. On this day patient developed a troublesome cough. On the next day (October 24) the sputum was blood-streaked. October 26, "Patient raised quite a considerable amount of blood." The cough and bloody sputum lasted for several days. On November 6, there was pain in the left groin and leg and two days later "tenderness in calf and along course of the long saphenous vein." Later still the leg became edematous. The temperature, which had been normal, rose for two days with the appearance of the signs of phlebitis.

CASE 2.—W. B., male, aged 26. No. 2806. Admitted Aug. 31, 1899, on ninth day of disease. Five days later (September 4) patient had a chill at noon and three hours later became very cyanotic, vomited, had a rapid, weak pulse and began to cough up blood-streaked mucus. September 12, had chill and became cyanotic. September 13, two chills. Over lower part of right chest behind, dullness, bronchovesicular breathing and crepitant râles. September 14, "Patient cyanotic, pulse very weak." During the next three days several chills. September 19, pain in right leg. September 20, signs of fluid over lower part of right chest behind. Pain, tenderness and swelling appeared in right thigh and calf. On September 27, pus was evacuated from right thigh, and on October 12, pus was discovered in right calf. Later there developed pain, tenderness and redness along the lower part of the inner side of the leg which persisted for a fortnight or more and gradually disappeared. The chest signs slowly disappeared and the patient recovered.

CASE 3.—M. B. W., female, aged 24. No. 2987. Admitted Oct. 12, 1899, on fifth (?) day of illness. Severe course with persistent nausea and vomiting. October 17, patient had a chill with sweating, and soon afterward began to have severe abdominal pain. On the following day the pain was very severe and was localized over the right side of the chest. October 23, pain appeared in left leg and popliteal space. October 27, pain in left side of chest. October 29, pain began in right leg. November 2 and 4, chills. Pain in legs continued and on November 11 there was tenderness along the course of the femoral vein in both thighs. On the evening of November 17 there was a chill followed by sudden, severe pain referred to the region of the right shoulder and the patient was delirious through the night. All the symptoms gradually subsided and the patient recovered.

* CASE 4.—D. P. T., male, aged 24. No. 6593. Admitted Nov. 23, 1901, on twenty-first day of illness. The patient was delirious and very sick. Over the left lower lobe there was an admission dullness, diminished breathing and subcrepitant râles. On November 28 there was bronchial voice and breathing at the level of the angle of the scapula and signs of fluid below this. November 29, "area of consolidation unchanged. Signs of fluid much less." December 3, "Pain and tenderness along course of both internal plantar nerves." This pain in soles of feet

was troublesome for some days. On the night of December 16, patient developed a troublesome cough and on following day began to have very severe pain in right side of chest and in right shoulder, and the temperature rose from 100 to 104 F. The pain and cough continued through the night and next day over the right lower lobe there were signs of fluid and that evening twenty-five ounces of clear fluid were removed. December 23, "Patient complaining of pain in right leg and groin for several days. Tenderness is very marked over veins of thigh, where a cord can be felt." The phlebitis ultimately subsided without edema.

CASE 5.—M. M., male, aged 18. No. 8179. Admitted Sept. 21, 1902, on fifth day of illness. Ran a fairly severe course. No pulmonary signs or symptoms on admission. September 27, at 5 p. m., the patient began to have very severe pain over left lower chest and in epigastric region, and temperature rose to 105.8. Patient was delirious much of the time for several days. No definite signs in the chest. October 11, "Has improved very much. Mind quite clear. Complains of pains in left thigh and there is slight tenderness along course of the femoral vessels. For several days patient has been complaining of painful feet and his toes are very tender." October 13, "Complains of left arm being painful and is unable to bend elbow." November 15. Tenderness along course of femoral vein had disappeared, but toes still somewhat tender. Good recovery.

CASE 6.—W. C. G., male, aged 40. No. 8467. Admitted Nov. 17, 1902, on ninth day of illness. Very severe course; delirious much of time. November 21. Sudden pain in left chest, followed by coughing. November 22, 3 a. m. Sudden cyanosis and dyspnea. Dyspnea continued throughout day. Troublesome cough. During next three weeks much coughing and frequent sweats. Beginning December 12, frequent chills and sweats. December 15. Severe pain in right leg followed by signs of phlebitis in thigh and leg. December 20. Pain in right chest and great restlessness. More cough. December 26. Signs of phlebitis in left calf. Return of pain in right chest. January 4. Small area of dulness and a few crepitant rales in (right?) lung. Sputum streaked with blood. January 5. Patient developed signs of edema of the larynx and died in spite of a tracheotomy.

CASE 7.—J. D., male, aged 12. No. 9879. Admitted Sept. 6, 1903, on fourth day of illness. Ran severe course. September 13 and 14: intestinal hemorrhage. September 21. Area of dulness near angle of right scapula with bronchial breathing and voice and many coarse rales. The cough and signs of consolidation lasted several days. September 27. Complained of pain in left leg, most marked along inner side of thigh where there is tenderness but no cord to be felt. Next day the temperature rose and continued high for some days. October 1. "Consolidation clearing up. Toes of both feet are tender." October 5. Toes no longer tender; and tenderness along inner side of thigh has disappeared. No further symptoms.

CASE 8.—R. A. R., male, aged 27. No. 10,130. Admitted Nov. 14, 1903, on tenth day of disease. Ran a moderately severe course. Lungs normal on admission. November 16. Right wrist painful and tender. November 21. During the night there was sudden severe pain in right side, requiring anodynes. The pain continued through the day, without other physical signs. November 25. "Abundant fine pleuritic rales in right axilla and at right base." The pains and the signs of plastic pleurisy continued for several days. The pain, tenderness and redness of right wrist also continued and extended to the palm of the hand. December 5. "Right wrist and hand not swollen but still somewhat tender. Today there is pain and tenderness in the left popliteal space and the left calf is somewhat swollen." Later the thigh became swollen and tender along the course of the femoral vein and a tender cord could be felt in the popliteal space.

CASE 9.—J. M., male, aged 18. No. 14,283. Admitted to hospital Aug. 31, 1906, on fifteenth day of illness. Severe course. Slight cough on admission. "Lungs normal except for a few scattered rales." September 2. Chill at 4 p. m. with rise of temperature to 105.6 F.; at 8 p. m., a second chill; temperature 106.6 F., respiration 36, pulse 124. September 3. Chill at 8 a. m. and again at 7 p. m.

No cough, pain or expectoration noted. September 5. Chill. September 6. Pain referred to left shoulder. Slight resistance and tenderness in left upper quadrant of abdomen. Chill at 11 p. m. September 7. Chill at 7:30 a. m. Severe pain in left chest, relieved somewhat by strapping chest. September 8. "Patient has had three attacks of severe pain in left side, each time accompanied by profuse sweating. Many fine crepitations over left lower back and in left axilla, brought out after coughing." September 11. Pain gone. Signs of fluid over lower half of left chest, but needle inserted in two places revealed no fluid. September 12. Chill at 6 p. m., temperature 106.4 F., respiration 40, pulse 140. September 14. Chill at 6 p. m. September 17. Temperature normal. "At left base, dullness, diminished fremitus, a few râles and soft bronchial breathing." On September 18, 19 and 20 some elevation of temperature without apparent cause. September 23. Temperature up. Pain in left groin and tenderness from groin down inner side of thigh to popliteal space. September 24. Cough more troublesome. "Is raising bloody sputum today." Some dullness with diminished breathing and voice at right base.

The signs of phlebitis in the left thigh and leg lasted for some time. The leg became edematous and some weakness and foot drop were noticed when the patient attempted to walk. The patient made a slow but complete recovery.

CASE 10.—J. M., male, aged 28. No. 14,943. Admitted Feb. 18, 1907, on the fourteenth day of illness. Patient had a dry cough on admission and on evening of the same day spat up considerable bloody sputum. February 22. "Marked dullness over entire right lower lobe, diminished breathing and many crepitant and subcrepitant râles." Cough and bloody sputum continued for some days. February 25. Pulmonary signs unchanged. Sputum had become foul smelling and dark in color. A needle inserted in lower part of right chest behind withdrew thick, dirty-red, foul-smelling material. The signs of a gangrenous abscess in the lung gradually subsided and the temperature fell to normal. On March 15 patient sat up for first time. March 20. Marked signs of phlebitis in both legs; severe pain, tenderness and edema. Gradual recovery.

CASE 11.—S. B., male, aged 34. No. 15,227. Admitted April 14, 1907, on twenty-first (?) day of disease. On April 16 and 17 there are notes of abdominal pain and rigidity, but the position of the signs is not given. April 21. "Pain in the right side on breathing or coughing. A few friction sounds in right axilla. Below angle of right scapula there is dullness and diminished breathing." April 24. Right chest aspirated; 175 c.c. of clear fluid obtained. April 27. "Sputum brownish-red." April 30. "Sputum still bloody and foul smelling." On May 8, a needle inserted into right chest, posteriorly, revealed pus and patient was transferred to the surgical service and operated on for a pulmonary abscess. Patient was allowed up on June 9. and two days later there were signs of phlebitis in both legs, with marked edema. Slow recovery.

CASE 12.—J. S., female, aged 35. No. 15,687. Admitted to hospital July 30, 1907, on thirteenth day of illness. Ran a moderately severe course, the fever gradually falling so that on the twenty-second day (August 8) the temperature remained below 100 F. On August 9, at 8 a. m., patient had a normal temperature and felt well. At 8:40 a. m. she complained of acute pain in the region of the heart, became cold and blue and broke out in a cold sweat. She complained of three such severe attacks of pain within an hour. The pulse rose from 72 to 116, the respirations from 20 to 44, and the temperature from normal to 103.6 F. During the afternoon and evening there were frequent paroxysms of pain in left chest, the patient was cyanosed and cold, the pulse rapid and feeble. There was also rigidity of the upper part of the left rectus muscle with tenderness. During August 10 and 11 there was troublesome dry cough with more or less pain in left chest. Pleuritic friction sounds could be heard in the left axilla and there was a distinct pleuropericardial rub. August 12. "Patient still somewhat cyanotic. Dry cough and pain in left axilla still persists." August 13. Cough accompanied by blood-stained expectoration. Impaired resonance, feeble breathing

and many crepitant râles at right base posteriorly, and many crepitant râles in left axilla. August 14. "Sharp pain in right side of neck and right shoulder. Troublesome cough but no expectoration." August 17. Dull ache in left thigh and groin which next day extended to left calf. August 19. Sudden stabbing pain in right chest. August 20. Expectoration of bright blood which continued for several days. On August 26 there developed pain, tenderness and swelling along the course of the right femoral vein; the tenderness extended up along the course of the external iliac vein, and there was swelling and tenderness of the labium majoris on that side. August 30. Pain referred chiefly to sole of right foot. Later edema appeared in both legs. The chest signs gradually cleared up and patient made a good recovery.

CASE 13.—Mr. H., aged 50, was admitted Sept. 2, 1910, on second day of illness. Course mild and uneventful until September 19. He then developed a troublesome cough to which was added, on September 22, pain in left side of chest which, for a day or two, was very severe. On the night of October 6, he had a chill and, a few hours later, severe pain in the left scapular region and cough. The pain and cough lasted for some days. On October 10 he spat up some bright blood-streaked mucus and for several days afterward the sputum contained dark blood. On October 15 he began to have pain and tenderness in right leg which, two days later, extended to the thigh along the course of the femoral vessels. On October 26 the same symptoms appeared in the left leg and about the same time he suffered greatly for several days with pain in the lumbar portion of back. The phlebitis in both legs ran a long and severe course. The temperature, which had reached normal, rose abruptly on October 7 after a chill and continued high and irregular throughout the course of the phlebitis.

CASE 14.—L. C., male, aged 29. No. 20,379. Admitted Sept. 9, 1910, on sixth day of disease. Mild course; uneventful until September 21; then sudden severe pain referred to right hypochondrium, rapid breathing and rigidity of upper part of right rectus muscle. That evening, "many crackling pleuritic râles in right axilla." One week later, "slight tenderness along inner side of right leg." No further notes on the condition of the legs. Discharged October 22. A few days later friends of the patient reported that he had "swelling of both legs below the knees."

CASE 15.—F. Z., male, aged 32. No. 20,513. Admitted Oct. 3, 1910, on ninth day of disease. Uneventful and rather mild course until October 22, when he complained of pain in left axilla and had "a few fine pleuritic râles" in the same region. On the next day the entire left leg seemed slightly swollen, was bluish in color and there was marked tenderness over the femoral vein. October 24, "marked tenderness in abdomen just above left Poupart's ligament." October 29. Tenderness in right thigh. November 1. "Pleural friction rub low in left axilla." When discharged there was still some edema of left leg.

CASE 16.—H. C., male, aged 21. No. 20,632. Admitted Oct. 25, 1910, on the eighth day of disease. Ran a moderately severe course. November 6. In afternoon the patient began to cough severely and continued to do so for a number of days. November 13. Complained of pain in side of chest on breathing. "Low in left axilla and posteriorly over left lower lobe are scattered coarse friction rubs." November 22 to 26. Intestinal hemorrhages. The temperature, after having been normal for two weeks, rose abruptly on December 7 and continued fairly high for a fortnight or more. On December 11 signs of phlebitis appeared in the right thigh and later showed also in the right calf. There was no edema.

CASE 17.—Mrs. L., aged 43. Admitted Dec. 18, 1910, on about the tenth day of disease. Moderate initial course followed by equally long "relapse." For about one week, beginning December 24, patient coughed much and had bloody expectoration. Later a few fine râles could be heard in both axillæ and in both bases behind. January 22 patient began to complain of pain in left arm. On January 27, pain began in right leg and a few days later in the left leg. The pain was

especially severe and protracted in the left leg where there was marked tenderness over the lower third of the anterior surface external to the tibia. At the time of discharge there was still slight edema of the foot and ankle.

CASE 18.—A. C., female, aged 37. No. 180,098. Admitted Nov. 24, 1911, on eighth day of illness. Moderate course. Temperature gradually falling and patient conscious and comfortable when at 9 p. m. on December 4 (eighteenth day) she complained of sharp pain in left side of chest. The pain continued next day but the signs in the chest were negative except for many fine râles at the end of inspiration. Patient spat up a small amount of bright blood. December 7, "Still spitting up a small amount of bright blood occasionally. Still no definite signs in chest." No pain or tenderness along course of veins of legs. December 8. Still coughing. In a. m. complained of pain in right heel. Later in the day there was slight pain in right knee. "Still no signs of phlebitis." The temperature, which had been below 100 F. for some days, rose in the afternoon to 104 F. and remained high for four days. December 9. Slight tenderness over position of Hunter's canal and in popliteal space of right leg. December 12. Patient complained of more pain in left side of chest. December 13. Cough much worse. Sputum again contained bright blood. Pain in left knee. "No signs of phlebitis on that side." December 14. Tenderness over Hunter's canal on left side. December 15. Severe pain in left side of chest. At left base, dulness and many fine râles. The cough and bloody sputum continued for several days longer. The phlebitis of both legs lasted for some time and subsided without edema.

CASE 19.—H. P., physician, aged 24. Onset June 9, 1910. Moderately severe course which was uneventful until the evening of twelfth day (June 21) when he was awakened by sudden, severe, thoracic oppression and a feeling of suffocation. He had dyspnea, cyanosis, cold sweat, a rapid, thready pulse and all the indications of alarming collapse. On the following day these symptoms had somewhat subsided. Examination of the chest was negative. June 23. Symptoms subsiding. Lungs negative except for diminished breathing and crepitant râles at angle of left scapula. In the afternoon began to have pain in left side of chest which on following day (June 24) became very serious. Very slight cough. No signs of phlebitis. June 26. Began to expectorate mucus mixed with dark blood. June 28. Sharp pain in right side of chest. June 29. Soreness in calf of right leg which, on following day, extended along the course of the femoral vein in thigh. The bloody sputum and cough continued for some days longer. July 5. Some pain in left calf. No further symptoms until July 14 when signs of phlebitis in left femoral vein appeared. The signs of plastic pleurisy in the left chest slowly disappeared and patient made a good recovery.

PULMONARY EMBOLISM AFTER THE APPEARANCE OF SIGNS OF PHLEBITIS

CASE 20.—W. E. S., male, aged 25. No. 1572. Admitted Dec. 4, 1898. Typhoid began in Porto Rico on October 8. Improved until November 13, when right leg became tender and swollen. This improved and patient left hospital. Two days before entrance to New York Hospital (December 2) the left leg became swollen and tender in the calf and on the following day, he had pain in left chest near his heart. On admission there was dulness and diminution of voice, breathing and fremitus at the left base and signs of phlebitis in the left leg. Recovery.

CASE 21.—H. W. W., female, aged 25. No. 2966. Admitted Oct. 7, 1899, on tenth day of illness. Severe course. October 14. Pain and tenderness along course of femoral vein in right thigh. Chills October 17 and 18. October 22. Very severe pain in left side which was followed by signs of pleurisy with effusion in left chest. October 23. Signs of phlebitis in left leg. Later edema of both legs.

CASE 22.—J. L. L., male, aged 26. No. 6393. Admitted Oct. 14, 1901, on sixteenth day of illness. On day before admission began to have severe pain in left thigh and leg and on admission showed well marked signs of femoral phlebitis. October 21. Soreness and tenderness in left heel, which lasted several days. October 23. Sudden change for the worse, with very rapid pulse and breathing.

October 24. Pain in right side of chest, with many friction sounds. October 27, Chill, with rise of temperature and labored breathing. Over lower part of right chest, flatness and diminished breathing, voice and fremitus. October 30. Small amount of fluid obtained from right chest. October 31. Signs of phlebitis in right leg. Very severe pain and tenderness in foot and heel which lasted some days. November 17. Sudden death, due probably to pulmonary embolism. No autopsy.

CASE 23.—S. H. C., male, aged 32. No. 9892. Admitted Sept. 8, 1903, on fourth day of illness. Very severe course. September 14. Pain in left popliteal space. September 18. Chill. September 23. Slight edema of left ankle. Tenderness and swelling of right calf. September 25. Severe chill. September 27. Chill. Dulness and many crepitant râles at left base posteriorly. September 28. Coughing. Two chills. Signs of consolidation at left base more distinct. October 9. Still signs of phlebitis in both legs. October 11. Two profuse sweats. October 12. Chills. Slight dulness and many crepitant râles over upper part of left lower lobe. Signs of fluid at base. Small amount of bloody fluid aspirated.

CASE 24.—Miss H. P., aged 25. No. 13,748. Admitted April 6, 1906, on seventh day of illness. Long, severe course. April 21. Began to complain of painful and tender toes, also of pain in both legs, but especially in left leg. April 23. Tenderness in right groin below Poupart's ligament. April 25. Cough and expectoration with râles at base of right lower lobe. Between April 26 and May 22 patient had eight severe chills with fever of markedly remittent type. During most of this time she suffered greatly from tenderness and pain in the toes. May 6. Frank signs of phlebitis in left leg and later in thigh. May 22. After a chill patient had a violent attack of coughing and complained of severe pain in left chest. For several days thereafter severe pain in left chest and left upper quadrant of abdomen. Irregular temperature continued for a fortnight longer.

CASE 25.—V. A., male, aged 42. Admitted Feb. 8, 1910, on sixth day of illness. Long severe course. February 19. Chill and later pain and tenderness over left femoral vein. Up to that time he had had no cough whatever. That night he was disturbed several times by coughing attacks which ceased next day. February 26. Chill, high temperature and signs of phlebitis of right femoral vein. March 5. Sudden, severe pain in right chest, cough, bloody sputum, dulness and râles at right base posteriorly. Later signs of consolidation in right lower lobe became more distinct. Cough and expectoration of blood lasted for two weeks. Slight chills with rise of temperature on March 15 and 25. On March 15 patient complained of great tenderness in toes of both feet, which continued for several days. Later edema of both legs. No rise in leukocytes.

CASE 26.—M. P., male, aged 23. No. 20,248. Admitted Aug. 22, 1910, on eleventh day of illness. Moderate course and uneventful convalescence until September 20. Patient had been up and about ward for several days and on this day temperature began to rise. On the following day there was pain in left thigh but no other indications of phlebitis. Later in the day there developed pain in right side of chest, made worse by deep breathing, and a few friction rubs could be heard in the right axilla. The pulmonary symptoms soon disappeared. All the usual symptoms of femoral phlebitis developed rapidly and lasted for two weeks.

CASE 27.—D. C., male, aged 23. No. 178,211. Admitted July 20, 1911, on fourteenth day of illness. He then complained of pain in the calves of the legs, especially the right, and there was marked tenderness of the muscles of the right calf and in the right popliteal space, and slight tenderness over the same areas in the left leg. From July 19 to 22 he complained also of pain and tenderness in both forearms. July 26. Severe coughing attacks throughout night. August 6. Pain in left side of chest. August 17. Two severe chills. August 18. Tenderness and palpable cord in right femoral region and in popliteal space and swelling of tissues of calf. August 19. Suddenly developed labored respiration with cough and blood-streaked expectoration. These symptoms continued until August 22 when he died. No autopsy.

CASE 28.—A. M., female, aged 25. No. 178,318. Admitted July 29, 1911. Patient had been ill for four weeks but had not gone to bed. On admission the dilated and tortuous superficial veins on the inner and anterior aspects of both legs and thighs were thrombosed, dark in color and tender to pressure. August 7, the patient suddenly became restless and dyspneic, complained of pain in the chest, and, later in the day, showed at the base of the right axilla, an area of diminished breathing over which were many fine râles. The pulmonary symptoms continued; the signs remained unchanged and three days later the patient died. No autopsy.

CASE 29.—B., male, aged 21. No. 178,517. Admitted Aug. 10, 1911, on sixth day of disease. Very mild initial course. After temperature had been normal for nearly five weeks it began, September 27, a step-like ascent, accompanied by general malaise and pains in the back and limbs. October 4. Tenderness over right femoral and popliteal veins and pain in calf. October 8. Had restless, sleepless night and complained of pain in chest. No cough. The signs of phlebitis gradually disappeared. The fever lasted a considerable period. There were no further pulmonary symptoms.

PHLEBITIS WITH PULMONARY SYMPTOMS OF DOUBTFUL NATURE

CASE 30.—P., male, aged 22. Admitted Nov. 20, 1897. Pulmonary signs at one base, with rise of temperature after defervescence. One month later frank signs of bilateral femoral phlebitis.

CASE 31.—H., female, aged 26. Admitted Dec. 9, 1897. Pulmonary signs at right base late in disease. Rise of temperature and rapid pulse. Three weeks later phlebitis of right femoral vein.

CASE 32.—H. W. L., male, aged 35. No. 5,341. Early pulmonary symptoms (severe cough and blood-streaked, frothy sputum). Later extensive phlebitis of both legs and right arm.

CASE 33.—C. S., female, aged 23. No. 8,695. Slight early pulmonary symptoms, probably not embolic. Two weeks later phlebitis of left femoral vein.

CASE 34.—D. E. D., male, aged 24. No. 13,097. After defervescence sudden cyanosis followed by rise of temperature and pain in region of diaphragm on left side. Five days later phlebitis of right external saphenous vein.

CASE 35.—G. S. B., female, aged 20. No. 14,095. Very severe course; patient delirious much of the time. Between July 19 and 26 troublesome cough with slight expectoration. July 26, 6 a. m., sudden cyanosis and collapse. July 28, "very free expectoration." July 29, "Complains of toes being painful." August 12, temperature after having been normal for five days, began to rise. August 14. Troublesome cough. August 17. Pain in right leg above foot. August 29. Severe pain in left leg, with rise of temperature. Later signs of phlebitis in both legs.

CASE 36.—A. W., female, aged 28. No. 16,313. During fifth week troublesome cough with râles, especially at right base. Two chills. Ten days later phlebitis of left femoral and calf veins.

CASE 37.—J. T., male, aged 32. No. 176,408. During defervescence troublesome cough for two days. Five days later signs of left femoral phlebitis with chill and high temperature.

PULMONARY SYMPTOMS SUGGESTIVE OF EMBOLISM WITHOUT EVIDENT PHLEBITIS

CASE 38.—M. K., female, aged 24. No. 2,045. Admitted March 13, 1899. Average uneventful course. At end of defervescence sudden, severe pain in right side of chest. Three days later severe pain in toes of both feet, lasting several days. No other signs of phlebitis.

CASE 39.—J. D., female, aged 53. No. 2,807. Admitted Aug. 31, 1899. Normal and uneventful course until September 24; then at 2 a. m. sudden collapse with rapid breathing, weak pulse and cold sweat. Gradual improvement. October 1,

sudden, severe pain in left side of chest, requiring morphin. Next day, dulness, bronchial breathing and crepitant râles over lower part of left lung behind. Signs disappeared in five days. October 8, severe pain in right hypochondrium. October 18, severe pain in right side of chest, lasting several days. Temperature up during each of the pulmonary attacks. No notes indicating phlebitis.

CASE 40.—A. P., female, aged 32. No. 2,888. Admitted Sept. 18, 1899. During fourth week chill, and on following day dulness, bronchial breathing and many râles over right lower lobe posteriorly. Two more chills on next day. Three days later sudden death. No mention of phlebitis. No autopsy.

CASE 41.—S. N., male, aged 19. No. 4,567. Admitted Oct. 7, 1900. Severe, protracted course. Temperature reached normal November 9. Rose abruptly November 15, without apparent cause and remained up for several days. December 1, chill with rise of temperature to 106 F.; down next day. December 3, two chills. December 5, sharp pain in right side of chest, cough and many fine râles at right base and in lower part of right axilla. Pain, cough and pulmonary signs lasted for ten days. Temperature high and irregular for some days longer and then fell gradually. No mention of phlebitis.

CASE 42.—J. N., male, aged 34. No. 6,355. Admitted Oct. 7, 1901. Ran a moderate course, the temperature reaching normal on October 20, and remaining so until October 23. On this day it rose somewhat. On the next it reached 103 F., and there was pain referred to the upper part of the abdomen. On October 25 the pain was localized in lower part of left axilla and a pleuritic friction rub was present. October 28, chill. October 29, temperature still high, troublesome cough and signs of a small area of consolidation near spine of left scapula. On the following day most of these signs had disappeared. Temperature reached normal on November 4. No mention of phlebitis.

CASE 43.—T. C., male, aged 26. No. 8,233. Admitted Sept. 30, 1902. General condition good; lungs clear. On twentieth day (October 5) pain in left side of chest and friction rub. Two days later signs of fluid. Turbid, serous fluid removed from left chest. More fluid removed on October 10 and 12. October 13, 5 p. m., patient died, apparently suddenly and unexpectedly. No autopsy. No mention of phlebitis.

CASE 44.—E. N., male, aged 26. No. 8,480. Admitted Nov. 20, 1902. Late in the disease sudden pulmonary signs with cough and bloody sputum. Then a "relapse," during which there were several chills and sweats. No notes indicating phlebitis.

CASE 45.—K. E., female, aged 43. No. 8,872. Admitted Jan. 31, 1903. Developed typhoid while in hospital. On thirteenth day (March 22) cough, expiratory grunt and small area of dulness above angle of left scapula. Several days later signs of consolidation at right base. Some time later, after temperature had reached normal, had a "relapse" with slight rise in leukocytes (10,000) but no notes to indicate presence of phlebitis.

CASE 46.—R. R., female, aged 26. No. 9,115. Admitted March 14, 1903. Severe but uneventful course. Temperature reached normal April 18. One week later temperature rose again without discoverable cause. Leukocytes 9,000. May 4, sudden onset at night of severe pain in left hypochondrium. This pain lasted several days, was made worse by deeping breathing or coughing. The fever continued for some days after subsidence of the thoracic symptoms. No other indications of phlebitis.

CASE 47.—W. K., male, aged 27. No. 9,979. Admitted Oct. 3, 1903. Fairly severe course. On eighteenth day (October 5) sudden, severe pain in right axilla, followed next day by friction sounds in the same region. These signs lasted for ten days. Gradual defervescence. No notes indicating phlebitis.

CASE 48.—E. B. A., female, aged 19. No. 10,002. Admitted Oct. 7, 1903. Moderate course. Temperature had been almost normal for several days when on

October 18, it rose again and ran a high and irregular course for some weeks. October 20. Severe pain in right side of chest and many fine râles in axilla. Next day cough and bloody sputum. Leukocytes 19,000. October 25, still spitting up blood. Signs of consolidation in right interseapular region. October 26. Sudden collapse with pallor, feeble pulse, etc. October 27. Severe pain in right upper quadrant of abdomen, with course friction rubs at base of right lung. Cough and bloody sputum. November 9. Severe pain in *left* side abdomen, with pleuritic râles in left axilla. Cough with occasional bloody sputa continued some days longer. Eventual recovery. No notes to indicate phlebitis.

CASE 49.—C. W., female, aged 24. No. 10,181. Admitted Nov. 27, 1903. Mild course. By December 5, temperature had fallen to about 100 F. December 6. Sudden pain in back, difficulty in breathing and rise of temperature. The next day the pain had become localized in left side of chest and was intense. Temp. 105 F., respiration 48, pulse 140. Leukocytes 13,000. December 8. Bronchial breathing and voice over upper part of left lower lobe, with dulness, diminished breathing and fine râles at the base. By December 11, the signs of consolidation had disappeared and the general condition was much improved. Two weeks later patient began to have small, bloody, mucous stools with much pain and tenesmus (thrombosis of hemorrhoidal veins?). No other indications of phlebitis.

CASE 50.—J. L., female, aged 16. No. 13,337. Admitted Dec. 28, 1905. Fairly severe course. Troublesome cough for several days during fifth week. Later an apparent relapse and during this, signs of pleurisy with effusion at left base. No leg symptoms.

CASE 51.—J. R. L., female, aged 28. No. 13,373. Admitted Jan. 4, 1906. Very severe course. Late in the disease signs of consolidation in right lower lobe, with chills and marked leukocytosis. Rapid resolution. No leg symptoms.

CASE 52.—L. I., male, aged 38. No. 13,440. Admitted Jan. 19, 1906. Mild attack. January 25. Began to have burning pain starting just below and inside left shoulder and extending down forearm to hand, with inability to flex thumb and index finger. From February 6, to February 13, profuse sweats every night. February 15. Sharp pain in right side of chest on breathing, with dry râles on inspiration. The temperature after being normal for a week began to rise on January 31 and remained elevated for three weeks. The pain in the arm lasted for several weeks.

CASE 53.—A. M., female, aged 22. No. 14,128. Admitted July 18, 1906. Moderate course. At end of fourth week, with temperature almost normal, pain, and signs of dry pleurisy in left side and rise of temperature. Ten days later (August 10) signs of dry pleurisy at base of right lung. August 13, sudden severe pain in left side of chest and left shoulder, with a few crepitant râles in left axilla. No further symptoms. Rapid recovery. No notes indicating phlebitis.

CASE 54.—L. G., female, aged 25. No. 14,211. Admitted Aug. 10, 1906. Moderate course and long relapse. Toward the end of this signs of consolidation at base of right lung. Death. No autopsy. No indications of phlebitis.

CASE 55.—W. M., male, aged 18. No. 14,528. Admitted Nov. 2, 1906. Moderate course. At end of fourth week, with temperature low but unsteady, symptoms of severe plastic pleurisy at base of right lung which lasted for one week. No notes indicating phlebitis.

CASE 56.—H. S., male, aged 21. No. 14,625. Admitted Nov. 26, 1906. Fairly severe course. During third and fourth weeks signs and symptoms of plastic pleurisy over lower half of right chest. Temperature reached normal about December 24, and remained so until January 1, when it rose suddenly to 104, remained high for several days and gradually fell to normal. No apparent cause for the rise. No notes indicating phlebitis.

CASE 57.—S. Q., male, aged 25. No. 14,830. Admitted January 21, 1907. Severe protracted course. At end of fourth week (January 28) with temperature falling, sudden, very severe pain in right chest with rise of temperature and signs

of consolidation in right interscapular region. No change in leukocytes (7,000). Temperature reached normal February 2, and remained down until February 7. It then rose rapidly to 104 F., remained high for one week and gradually fell. Later there was another transient rise. Nothing found to explain the temperature. No notes indicating phlebitis.

CASE 58.—I. M., male, aged 16. No. 14,903. Admitted Feb. 8, 1907. Moderate course, uneventful until February 19, at which time temperature had fallen almost to normal. Then sudden pain in left chest. A few hours later had a chill with moderate rise of temperature. Four days later, when temperature had again become normal, dulness at left base with rales. Two days later sudden transient rise of temperature to 105 F. without apparent cause. Rales persisted for some days. No signs of phlebitis.

CASE 59.—E. P., female, aged 26. No. 15,174. Admitted April 3, 1907. Severe course. On twentieth day (April 10) dulness, bronchial breathing and voice and crepitant rales over both lobes posteriorly. Signs lasted one week. Defervescence by lysis. No material rise in leukocytes. Slow convalescence. No signs of phlebitis.

CASE 60.—A. B., male, aged 27. No. 15,514. Admitted June 18, 1907. Rather mild course. Temperature reached normal on June 28, and remained so until July 2. Then pain in right axilla, cough and "brownish viscid sputum" with rise of temperature. Later signs of fluid. After temperature had reached normal it rose again for a day or two without evident cause. No signs of phlebitis.

CASE 61.—C. A. H., male, aged 32. No. 17,579. Admitted Oct. 31, 1908. Moderately severe course. Temperature gradually fell to normal and remained down for four days; then (November 24) began to rise. Pain in left side, and dulness, diminished breathing and friction rubs at base of left lung. Signs of pleurisy and cough lasted two or three weeks. Temperature fell gradually. No notes indicating phlebitis.

CASE 62.—M. H., male, aged 40. No. 18,820. Admitted Sept. 23, 1909, on eleventh day of disease. Complained of pains in legs before admission. Slight pretibial edema. Uneventful course until October 20. Temperature running below 101 F. Then rise of temperature and pain in lower part of left chest with, later, pleuritic friction rubs over same region. No signs of phlebitis.

CASE 63.—G. P., male, aged 24. No. 179,816. Admitted November 5, on twenty-second day of illness. Severe course, uneventful until November 15. Then sudden pain in right axilla, followed by friction sounds, cough and abundant "frothy, blood streaked sputum." November 20. Pain and friction sounds now in *both* axillae. Cough and bloody sputum persisted. Temperature continued high and irregular. Two weeks later signs of small pulmonary abscess in left lower lobe. Operation. Death. No autopsy. No evidence of phlebitis.

THE RELATION OF THE LATE MULTIPLE CHILLS OF TYPHOID TO THROMBOPHLEBITIS

In studying the cases of typhoid with a view to ascertaining the mutual relations between phlebitis and pulmonary and pleural complications, it soon became evident that in the cases complicated by phlebitis the occurrence of chills was so frequent as to call for investigation; more especially, as in most cases such chills were multiple. These multiple chills of the later weeks of typhoid have never received a satisfactory explanation. After eliminating the rare instances of true malarial chills, and those seen in the course of pyelitis and other recognizable complications, there remain a considerable number of cases of protracted typhoid

in which the latter weeks of the course are punctuated by a succession of abrupt violent rises of temperature, associated usually with chills and followed often by sweats. For these disturbing symptoms usually no adequate cause can be found, and, although the blood-cultures are uniformly negative and the leukocytes frequently show no significant change, these obscure cases are apt to be regarded as instances of post-typhoid sepsis. A further characteristic feature of these cases, in my own experience, is that they all ultimately recover.

Among the total number of cases of typhoid fever reviewed, multiple chills occurred in twenty instances. In sixteen of these twenty cases (80 per cent.) there were well marked signs of thrombophlebitis. In every one of the four cases in which no signs of phlebitis were observed there were pulmonary symptoms strongly suggestive of pulmonary embolism (see Cases 40, 41, 44 and 51). In ten of the sixteen cases with phlebitis, also, there were symptoms of pulmonary embolism. Sometimes the chills would coincide with the onset of the pulmonary symptoms; occasionally they would synchronize with a fresh exacerbation of the phlebitis, but frequently they occurred without other symptoms and without apparent reason. In seven cases all the chills occurred before any of the signs of phlebitis were apparent. Four of the cases have already been cited (Cases 2, 9, 24 and 36); the others follow:

CASE 64.—C. G., male, 26 years old. No. 8,488. Admitted Nov. 22, 1902, on sixth day of illness. Moderate course. By November 27 temperature had fallen to 100 to 102 F. This continued until December 3 when temperature began to run higher. Chills occurred on December 7, 8, 10, 11 and 12. On December 31 patient complained of pain in calf of right leg and three days later there was tenderness over the calf, in the popliteal space and over the upper portion of the femoral vein. The temperature which had been about normal for some days began to rise on January 1 and remained elevated for two weeks. Meantime there were symptoms of extensive phlebitis of the right thigh and leg with, ultimately, slight edema. No pulmonary symptoms.

CASE 65.—C. K. W., male, aged 48. No. 12,626. Admitted June 21, 1905, on fifteenth day of disease. Fairly severe course. Between July 1 and 4 there were five chills, occurring without known cause, and during this time the leukocytes ranged between 4,000 and 5,300. On July 7 the right leg became painful and swollen and there was tenderness over the course of the femoral vein. On July 12 the left leg became similarly involved. No further chills, no pulmonary symptoms.

CASE 66.—J. V., male, aged 16. No. 17,160. Admitted July 19, on seventh day of illness. Moderately severe course. On July 22 and 23 severe intestinal hemorrhages. On July 24, 25 and 29 chills without apparent cause. August 2, "Lungs clear except for scattered râles." Course uneventful until August 23 when there appeared signs of phlebitis in left groin. These later involved the left leg and were associated with edema. No pulmonary symptoms.

In six instances the chills took place both before and during the obvious manifestation of phlebitis, Cases 3, 6 and 13, and the following:

CASE 67.—J. H. J., male, aged 24. No. 2,634. Admitted July 26, 1899; on twentieth day of disease. Severe course. Very sick and delirious for a number of days. Between July 31 and August 15 there were six chills. On August 17

symptoms of phlebitis appeared in left leg and a few days later in the right leg. Further chills occurred on August 27 and 29 and September 2 and 6. The phlebitis ran a long, severe course. No notes of any pulmonary complications.

CASE 68.—O. H., male, aged 32. No. 4,110. Admitted July 4, 1900; on fourteenth day of disease. Moderate course. July 15 chill with rise of temperature to 105 F. During next three days gradual fall in fever to 100 F., then (July 19) chill and rise to 105 F. After that the temperature continued high for some days. July 23, pain and tenderness over upper part of left internal saphenous vein and five days later signs of involvement of femoral on same side. Between July 24 and 31 five further chills. Slow convalescence. No pulmonary symptoms.

CASE 69.—R. R., female, aged 20. No. 12,894. Admitted Aug. 29, 1905, on sixth day of disease. Fairly severe course. September 13 (Nurse's note) "Complaints of pain in feet. Left foot and ankle considerably swollen." From September 13 to October 1 patient had almost daily chills without obvious cause. Blood cultures were sterile, there was no rise in the leukocytes and physical examination of the chest was negative except for scattered sibilant and sonorous sounds. On September 19 a tender, elongated mass could be felt over the upper part of the left femoral vein and there was slight edema of both ankles. The symptoms soon subsided and it was not until October 25, after the patient had been sitting up for a few days, that frank symptoms of milk leg appeared. No pulmonary symptoms.

In three cases the chills did not occur until after the phlebitis had declared itself. (Cases 21, 23 and 25).

In view of the fact that, in 80 per cent. of the cases of typhoid marked by the occurrence of multiple chills of unknown cause, there was present also thrombophlebitis, and of the further fact that in all of the few remaining cases, in which no phlebitis was recognized, there occurred symptoms suggestive of pulmonary embolism, it is difficult to escape the conclusion that these obscure "post-typhoid" chills bear some very direct relation to the thrombotic process in the peripheral veins. Just what that relation is, in every case, it may not be easy to say. Such rigors are probably not always due to the same cause. It is not uncommon for a chill to accompany the onset of symptoms of phlebitis of a large vein or to mark the sudden extension of such a phlebitis; but these are usually only single chills and this explanation fails entirely to account for the very characteristic type of cases we are considering in which chills may have been occurring almost daily for two or three weeks before any symptoms of phlebitis have appeared. A good many of the chills occurred simultaneously with the onset of symptoms of pulmonary embolism, but in these same cases some of the chills would take place *without* such pulmonary symptoms, and the question arises as to whether a rigor may not at times be the only recognizable symptoms of the lodgment of a tiny embolus. Gerhardt,¹² in his classical description of the hemorrhagic infarct, says: "The act of embolism can pass almost or quite without symptoms when small fragments of clot enter a sound lung or where marked dyspnea already exists." He also speaks of a chill as a

12. Gerhardt: Der hämorrhagische Infarct. Volkmann's Saml. klin. Vortr., 1875, No. 91.

frequent symptom of embolism. Even on the assumption, however, that some of the chills which appear without accompanying pulmonary symptoms may be due to tiny emboli, the problem does not seem to be altogether solved; for occasionally a case is met with in which, although there are many chills, there are no pulmonary symptoms with any of them. It seems very unlikely that twelve or fifteen attacks of pulmonary embolism should occur without some of them presenting characteristic symptoms or physical signs. For such cases it must be acknowledged that there is, at present, no satisfactory explanation.

The literature contains a good deal of evidence in support of the view that the late, multiple chills of typhoid bear some constant relation to thrombophlebitis; although this relation appears never to have been fully recognized. The reason for this seems to lie in the fact that the chills often begin two or three weeks before the usual symptoms of phlebitis appear. Herringham¹³ recorded six cases of multiple chills. In four of these the existence of thrombosis was recognized and in one other the symptoms as described strongly suggest thrombosis. Saw¹⁴ reports two typical cases of "septic" chills, in both of which there was venous thrombosis and in one also, a late and severe pulmonary embolism.

Leclerc¹⁵ and Howland¹⁶ each report a case of multiple chills accompanied by thrombophlebitis.

Thayer³ found that in 28 per cent. of his cases of venous thrombosis complicating typhoid there were chills, and adds: "In the past two years I have seen in consultation three further cases in which otherwise unaccountable chills during convalescence from typhoid fever were followed by a complicating thrombosis."

THE RELATION OF THE SYMPTOM OF "TENDER TOES" TO THROMBOPHLEBITIS

The study of the cases of phlebitis complicating typhoid fever brought out the further fact of the frequent association of such cases with the interesting symptom known as "tender toes." This condition of painful and exquisitely tender toes is, as is well known, an occasional complication of typhoid and always appears late in the disease or during convalescence. It is commonly regarded as a neuritis of the plantar nerves although, in many instances, the transient character of the symptoms, as well as the lack of trophic changes, suggests that the process can

13. Herringham: On Rigor and Collapse in Typhoid Fever. *St. Bart's Hosp. Rep.*, 1896, xxxii, 107.

14. Saw: Septic Phlebitis and Thrombosis of the Femoral Vein Complicating Typhoid Fever. *Med. Press and Circ.*, 1897, lxiv, 453.

15. Leclerc: *Fièvre typhoïde, etc.*, Lyon méd., 1889, lxii, 289.

16. Howland: A Case of Typhoid Fever with Repeated Chills. *Med. News*, 1904, lxxxv, 820.

hardly be an actual neuritis. Among the 1,540 cases of typhoid reviewed this complication is recorded twenty-two times. In twelve of these cases (55 per cent.) there was also the complication of phlebitis of the legs. In seven of the cases the tenderness of the toes was complained of before the appearance of the symptoms of phlebitis; in five cases the signs of phlebitis appeared first. Nine of these twelve instances of the association of tender toes with manifest phlebitis have already been cited (Cases 4, 5, 7, 12, 22, 24, 25, 35 and 69). The remaining three are given below:

CASE 70.—F. B., male, aged 21. No. 1,278. Admitted Oct. 4, 1898, on tenth day of disease. Average course. Temperature reached normal October 28. On October 20 first complained of "tenderness of toes." Allowed up in chair on November 2. Next day pain in left leg and on following day pain, tenderness and swelling in left calf. No temperature with the phlebitis.

CASE 71.—F. P. S., male, aged 37. No. 11,735. Admitted Dec. 8, 1904, on fifteenth day of disease. Moderate course. Temperature fell rapidly to 100 F. on December 24, then rose slightly for five days, then fell to normal. From December 27 to 31 patient had pain and tenderness in left foot and toes. January 2 signs of phlebitis in left thigh and calf.

CASE 72.—P. E. C., female, aged 19. No. 17,290. Admitted Aug. 19, 1908, on tenth day of disease. Temperature reached normal by August 27. On August 30 the temperature rose slightly and remained somewhat elevated for several days. On August 31 there was severe pain in the left groin and upper part of thigh with all the usual symptoms of femoral and popliteal phlebitis. For the period of a week after the onset of these symptoms there was pain and tenderness in the sole of the left foot, toes and heel.

In addition to the above-mentioned cases of tender toes there were several cases of phlebitis in which pain and tenderness of the heel were the first indications of phlebitis in that leg.

TENDER TOES WITHOUT SIGNS OF PHLEBITIS

An analysis of the ten cases of tender toes in which there was none of the usual evidences of phlebitis shows that in seven of these there was at the time of the appearance of the painful and tender toes an irregular and unaccountable post-typhoid febrile movement. In one of the three remaining cases there were the symptoms of pulmonary embolism.

CASE 73.—W. H. S., male, aged 24. No. 1,043. Admitted Sept. 5, 1898. Severe course. Temperature reached normal on September 20. On September 22 began to complain of severe pain and tenderness of feet and toes which lasted for some days. September 24, temperature rose to 102 F. and fell to normal next day. Later patient ran a high and irregular temperature for twelve days, with no apparent cause.

CASE 74.—M. K., female, aged 24. No. 2,045. Admitted March 13, 1899. Average course. Temperature reached normal March 26. On March 24 sudden pain in right side of chest. March 27 and for several days thereafter pain and tenderness of toes of both feet. No temperature. No notes indicating phlebitis.

CASE 75.—T. K. B., male, aged 32. No. 6,278. Admitted Sept. 26, 1901. Prolonged but not severe course. Temperature reached normal by November 4. On October 29 there was noted "pain and tenderness along the course of both internal plantar nerves, especially the left." No evidence of phlebitis.

CASE 76.—B. E., male, aged 28. No. 6,307. Admitted Oct. 1, 1901. Protracted course. Two early and small hemorrhages. On October 14, first complained of tenderness of feet, especially on pressure. Between this date and November 17 there are several references to the continued tenderness and pain in the feet. On the nights of November 4 and 5 there were severe paroxysms of coughing. On November 26 there were local applications to the legs—apparently because of pain. After October 16 the temperature ran a high and irregular course. On October 23 there was a sudden rise to 106.8 F. It reached normal first on November 11 but did not remain constantly so until November 30.

CASE 77.—B. B., female, aged 44. No. 6,374. Admitted Oct. 11, 1901. Short, mild course. On admission "slight edema of the extremities." Between October 21 and 24 severe pain and tenderness in toes and soles of both feet. No further symptoms.

CASE 78.—M. S., male, aged 24. No. 7,800. Admitted July 14, 1902. Moderate course. Defervescence complete by August 4. On August 11 began to have pain and tenderness in toes of right foot which lasted eight or nine days. With this there was a slight rise of temperature for three days. No other symptoms.

CASE 79.—B. S., female, aged 22. No. 9,828. Admitted Aug. 22, 1903. Long, severe course. Severe bronchitis during the early weeks. On September 6, first complained of tenderness of toes. September 8, slight edema of feet and tenderness low in the right iliac fossa but no tenderness over either femoral vein. The pain and tenderness in the toes was present almost constantly for the next two months. The temperature which had gradually fallen to about 100 F. began on September 17 to rise again and then ran a high and irregular course for the next six weeks without any local symptoms.

CASE 80.—C. G. F., male, aged 30. No. 12,904. Admitted Aug. 31, 1905. Course of average severity. During convalescence and with normal temperature complained for several days of tenderness of toes. No rise of temperature. No other symptoms.

CASE 81.—G., male, aged 14. No. 9,668. Admitted July 10, 1903. Fairly severe course. On twenty-third day first complained of soreness of toes and soles of feet. The tenderness and pain was very troublesome for four days and then disappeared. Later a short "relapse." No other signs of phlebitis.

CASE 82.—C. E., female, aged 20. No. 10,858. Admitted May 6, 1904. Mild, initial attack, followed by severe, prolonged relapse. During this complained of tenderness of toes and feet. Following this, prolonged, irregular, but not high temperature. No notes indicating phlebitis.

From the foregoing facts one is, of course, not justified in accepting as proven the causal relation between phlebitis and the symptoms of tender toes; and yet the association of the two conditions is much too frequent and striking to warrant the assumption that this association is merely a fortuitous one. It seems unlikely that thrombosis and inflammation of the small veins of the foot should of themselves produce the symptoms under discussion. It seems to me more probable that there is first a thrombosis of one or more of the veins in the region of the heel and that the subsequent periphlebitic exudate may in some cases be sufficient to irritate, or actually to cause, an inflammation of, the adjacent plantar nerves. A moment's reference to any good anatomical plate of the deeper structures of the sole of the foot will show how very close is the approximation of the two plantar arteries, with their *venae comites*, to the corresponding internal and external plantar nerves.

Especially at the heel, where the posterior tibial artery, with its veins, curves over the astragalus to reach the sole of the foot, the vessels and nerves are in very close contact. There also it seems likely that the angular bend in the veins may predispose to the development of thrombosis and phlebitis. This hypothesis receives clinical support from the fact that pain and tenderness of the heel are not uncommon symptoms in thrombophlebitis.

It seems to me quite possible that some or most of the cases of *localized* neuritis which complicate typhoid fever may be found to be due to periphlebitic inflammation from some adjacent thrombosed vein; for in all the extremities the deep vessels and nerves are generally found in close proximity to each other. In Case 9 of this series, in which there was phlebitis of the left femoral and popliteal veins, there was evidently an associated neuritis, as shown by the weakness of the anterior tibial group of muscles in the affected leg.

THE TEMPERATURE IN THROMBOPHLEBITIS

A febrile movement of some degree was present in all but about 10 per cent. of the cases of thrombophlebitis. In a majority of the cases the temperature rose with the appearance of the signs of thrombosis of a large vein. Not infrequently, however, the febrile movement began several days or even longer before any of the usual symptoms of thrombosis had appeared. Every possible variation, as regards time of appearance, duration, severity, type, etc., was encountered, in studying the behavior of the temperature in the cases of typhoid complicated by phlebitis. In a number of the cases there was fever for some days preceding the appearance of signs of phlebitis, but no fever afterward. In others the temperature rose only after the phlebitis had been manifest for several days. The vagaries of the temperature curve are well shown in the cases cited in the section relating to multiple chills. In a good many of the cases after the period of typhoid defervescence had become nearly or quite complete the temperature would rise again and then run a long and irregular course, in the midst of which, at some time, appeared the signs of venous thrombosis. Sometimes this post-typhoid fever was accompanied by chills; sometimes there were sudden, short rises of temperature without an accompanying chill and without apparent cause.

Such late and prolonged periods of fever are often regarded as relapses or recrudescences of the typhoid process, but it is not difficult I think to distinguish between a true relapse and the type of fever under consideration. In going over the temperature charts of a large number of cases of typhoid I have been led to the conviction that in all uncomplicated cases of typhoid the fever curve is strikingly uniform and constant in its general type, although varying much in its duration, its

severity, and to some extent, in the length of its periods of ascent and defervescence. Any radical departure from this familiar type usually indicates the existence of some complication, even though the complication may not always be readily discoverable. The same statements, I believe, apply to the true and uncomplicated relapse. There is the more or less gradual ascent, the period of continuous elevation and the period of defervescence; and the chart of such a true relapse bears little or no resemblance to the various types of post-typhoid temperature described above. Sudden, violent remissions or exacerbations; greatly prolonged, slight, febrile movements; the occurrence of chills, are all indications that the fever is not that of a true relapse, but is due to some complication or sequel. In such cases, when the various other possible complications have been excluded, there will usually be found sooner or later some symptoms to indicate the existence of a thrombophlebitis. Many of the sudden and transient rises of temperature seen during convalescence from typhoid and usually ascribed to errors in diet are unquestionably due to this cause. The fact that a febrile movement may have existed for two or three weeks before any signs of phlebitis of a large vein have appeared cannot be held to invalidate this view as to the association of the two conditions, for there is an abundance of evidence to show that the phlebitic process may remain latent, or nearly so, for a period of several weeks.

No entirely satisfactory explanation for the occurrence of fever in the course of a latent phlebitis can be given at present. Bock¹⁷ has recently shown by experiments on animals that the intravenous injection of some indifferent and sterile substance, such as paraffin, in a finely divided state, is regularly followed by some rise in temperature. It is possible that some of the elevations of temperature seen in the early stages of phlebitis may be caused by the separation of tiny fragments of the thrombotic material before the vein has become occluded. Whatever may be the true explanation, the fact is beyond question.

Vaquez,⁷ speaking of the behavior of the temperature in phlebitis, says: "We believe, for our part, that very frequently a notable elevation of temperature precedes the appearance of *phlegmasia alba dolens*, but that this elevation of temperature should be sought for not on the day, or the second day, before the first apparent manifestation, but often eight, ten or twelve days before."

THE LEUKOCYTES

In most of the cases there was some rise in the number of leukocytes, and some increase in the proportion of the polynuclear cells, at the time of the appearance of frank signs of phlebitis of a large vein. The

17. Bock: Ueber Fiebererscheinungen nach intravenösen Injectionen vornehmlich indifferenten Partikelschen. Arch. f. exper. Path. u. Pharm., 1912, lxxviii, 1.

increased leukocyte count varied from 10,000 to 26,000. In some cases there was no appreciable rise in the leukocytes at any time, and in many cases a leukopenia persisted for some time after the appearance of the first indications of involvement of the veins. The absence of a leukocytosis cannot, therefore, be used as evidence against the existence of venous thrombosis. The increase in the leukocytes seems to depend chiefly on the presence of a well-marked periphlebitis.

In the present article it has been my aim, not to cover every possible symptom and complication of thrombophlebitis as it is seen in typhoid fever, but to call attention to several interesting groups of symptoms not usually regarded as having any direct relation to venous thrombosis, and to attempt to demonstrate that such a direct relation does actually exist. But this study of the late complications of typhoid in relation to venous thrombosis brought to light a number of interesting and suggestive facts whose significance is not yet clear, and which have not been discussed here, but which, nevertheless, are worthy of study and elucidation. Indeed, it is hardly too much to say that the whole symptomatology of the later weeks of typhoid requires to be studied anew from the standpoint of the possible relation of the various symptoms to thrombophlebitis. For example, the relation of thrombosis of the veins of the mesentery and of the intestinal wall to the abdominal symptoms of typhoid is altogether unknown. The fact that in the routine, post-mortem examination of typhoid cases such thromboses are rarely if ever discovered, is by no means proof that they do not occur. Thrombosis of the smaller veins could readily pass unrecognized unless special attention were directed to their examination. In reading through the protocols of the cases complicated by phlebitis I have been struck by the frequency with which various obscure abdominal and intestinal symptoms occur. It is possible that some of the attacks of sudden abdominal pain, tenderness and distention which often closely simulate the symptoms of perforation; that some of the dysenteric symptoms; that some of the repeated, small intestinal hemorrhages, may have their origin in thrombosis of the small mesenteric veins.

Two other late complications of typhoid may be mentioned as being worthy of investigation as to their possible connection with thrombophlebitis. One is periostitis, which appeared in a number of the cases during the course of a phlebitis. The other is the rare complication of inflammation of the breasts. In a woman with thrombosis of the veins of the legs there appeared first in one breast and then in the other a phlebitis of one of the veins near the periphery, which was followed by an extensive periphlebitis, so that the condition might easily have been mistaken for a primary mastitis. One cannot but wonder if in all the

instances of so-called mastitis complicating typhoid the process may not have begun as a thrombosis of the mammary veins.

SUMMARY

The opinions set forth in the preceding pages may be briefly summarized as follows:

1. Thrombophlebitis is a much more frequent complication of typhoid fever than is generally supposed, and probably occurs in from 10 to 15 per cent. of all cases. Its development is gradual; its course frequently latent for many days, and its classical symptoms usually appear only at a late stage of the condition. The thrombotic process is apt to be much more extensive and more widely disseminated than the pronounced local symptoms would suggest.

2. Most of the pulmonary and pleural complications which appear late in the course of typhoid are due to embolism of branches of the pulmonary artery, and this in turn is due to a complicating venous thrombosis. Such emboli are usually small and their symptoms are frequently mild and transient. The emboli seem to arise chiefly from the freshly formed, friable thrombi in veins which have not yet become occluded; and their symptoms, in a majority of the cases, appear before the usual symptoms of phlebitis are observed.

3. The obscure, late, recurring chills of typhoid are regularly associated with venous thrombosis although the latter is frequently latent at the time of the appearance of the chills. Some of the chills are certainly related to the lodgment of pulmonary emboli.

4. The symptom of "tender toes" can be shown to be associated with thrombophlebitis, in a majority of the cases. The suggestion is made that this symptom may be due to irritation or inflammation of the plantar nerves, which is set up by periphlebitic inflammation from adjacent, thrombosed veins in the sole of the foot or about the heel.

5. Many of the unaccountable rises of temperature seen during convalescence from typhoid and most of the protracted and irregular types of "post-typhoid" fever are due to thrombophlebitis.

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THE PEPTOLYTIC POWER OF GASTRIC JUICE AND SALIVA WITH SPECIAL REFERENCE TO THE DIAGNOSIS OF CANCER *

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CHICAGO

I.

In 1909 Neubauer and Fischer inaugurated the use of the dipeptid, glycyltryptophan, for the detection of peptid-splitting power in stomach contents, with special reference to the diagnosis of carcinoma. Their report called forth a shower of comments. It is not necessary to give a detailed account of the work, since this has been done repeatedly. But it may be recalled that it was based on an idea of Friedrich Müller that stomach contents from carcinoma patients could carry protein cleavage beyond the point at which normal peptic digestion ceases, and that this power was due to the presence in cancer tissue of an enzyme which could be secreted into the stomach.

Emerson showed that malignant growths actually contain an enzyme capable of splitting protein beyond the albumose phase, and in greater strength than that seen in benign growths, normal tissues, or in blood. He found similar properties in gastric contents from cancer patients. This work was confirmed and extended by H. Fischer, and Neubauer and Fischer, who introduced the dipeptid glycyltryptophan as a reagent for the detection of peptid-splitting enzymes, and applied it in the study of a series of clinical cases which included twelve of carcinoma. The test consists in mixing glycyltryptophan with gastric juice, incubating the mixture and testing with bromin for the rose-violet color indicative of free tryptophan. They drew the following conclusions: 1. In carcinomatous stomach contents a ferment occurs, which, unlike pepsin, splits glycyltryptophan. 2. The ferment is destroyed by 0.36 per cent. hydrochloric acid. 3. The presence of the ferment is usable in diagnosis (*"ist diagnostisch verwendbar"*). Since certain later writers have asserted that the test has no diagnostic value, we call attention to the conservative wording of the original.

In the examination of contents from pathological stomachs they recognized, *a priori*, certain sources of error: 1. Occurrence of tryptophan in the stomach contents themselves. 2. Presence of peptid splitting bac-

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teria. 3. Presence of trypsin (pancreatic juice). 4. Presence of blood (erepsin).

Concerning *tryptophan in stomach contents as aspirated*, much had already been written by Erdmann and Winternitz, Glaessner and Volhard. The conclusions of these writers, confirmed by Neubauer and Fischer, were to the effect that tryptophan seldom occurs in normal cases; that it frequently occurs in carcinoma and at times in certain non-malignant conditions associated with low acidity, and in motor insufficiency even with high acidity. Neubauer and Fischer regard such contents as unsuitable for application of their test. Concerning *the influence of bacteria* they conclude that simple filtration of the contents through paper is a sufficient safeguard. *Reflux of pancreatic juice* interferes with the test, but since, save in cases of cessation of the outflow of bile, it seems hard to imagine reflux of intestinal contents into the stomach without bile, they advise testing for bile and discarding such specimens as contain it.

By the latter part of 1911 seven communications had appeared commenting on this work (Lyle and Kober, Ley, Kuttner and Pulvermacher, Weinstein, Ehrenberg, Oppenheimer and Pechstein). None of the writers attacked the principle of the test. All applied it to series of cases. All agreed that it was positive in most cases of cancer and negative in most normal cases. The reaction was observed, however, in non-malignant conditions associated with sub- or anacidity, and found negative in some cases of cancer. There was a manifest divergence of opinion as to the exact limits of its usefulness.

Lyle and Kober, Oppenheimer, and Pechstein reported in the main favorably; Weinstein objecting to the cost and stability of "*ferment diagnosticum*" (the commercial toluenized solution of glycytryptophan marketed by Kalle & Co., Biebrich a. R.), held that a direct bromin test for tryptophan in the stomach contents was simpler and more reliable than the glycytryptophan procedure. In so doing he reverted, apparently unconsciously, to the older idea of Volhard and Glaessner. He disagreed with Neubauer and Fischer on minor points, but came to generally favorable conclusions, especially as regards the direct test for tryptophan after a protein meal. Kuttner and Pulvermacher also objected to the use of glycytryptophan on the score of cost. They proposed using silk peptone instead and gauged its splitting by the observation of a precipitate of tyrosin under the microscope. They made eight parallel tests to establish the equivalence of the two procedures, and then, discarding the glycytryptophan method, made a series of observations with silk peptone. From the results so obtained they came to highly unfavorable conclusions. They coincide with the views of those who regard reflux of pancreatic juice as a common occurrence, and consider

the bile tests recommended by Neubauer and Fischer as inadequate for its exclusion. Ley and Ehrenberg had unfavorable experiences.

In a second communication published in 1911, the original writers review the literature up to that time. They point out that Kuttner and Pulvermacher employed a test differing from their own without adequately establishing the interchangeability of the two. Their analysis of the results obtained by all the above-mentioned writers indicates that out of all definitely proven cases of carcinoma studied, 84 per cent., and of the clinically diagnosed, 75 per cent., had shown positive reactions, while of the non-cancerous cases 14 per cent. were positive. They reiterate their cautions concerning blood and add that serum will also split glycytryptophan, in illustration of which they cite a case of uremic gastritis in which a positive test was encountered. They disclaim ever having entertained the view that the test was in any sense specific. With the possible exception of the Bence-Jones albumose reaction in myeloma, clinical chemical tests are not generally to be so regarded. However, they maintain that when properly performed and considered in conjunction with other data, this procedure is, as originally claimed, an aid in diagnosis.

In the meantime other reports have appeared (Hall and Williamson, Warfield, Koehlker and Sanford and Rosenbloom). Hall and Williamson find positive reactions in most cases of cancer, but not in all. They also find some positive reactions in non-cancerous conditions and suspend their judgment. Warfield, working with saliva obtained from the mouth with no aseptic precautions, and relying on the use of toluene and sometimes centrifugation for exclusion of bacterial action, finds that saliva mixed with a solution of glycytryptophan and incubated splits the latter, to give a positive tryptophan reaction with bromin. He suggests the possibility that bacteria may be responsible for this, but drops it with a negatively tending reference to Weinstein, and Neubauer and Fischer. Acids inhibit this action. The less acid in the stomach contents, according to Warfield, the greater the frequency of positive reactions, in benign as well as in malignant conditions. On the other hand, definitely cancerous contents with high combined acidities or with a relatively large amount of lactic acid are said to yield negative tests. He points out that although the presence of a peptid-splitting enzyme in cancer juice seems to have been demonstrated (and one may add in strengths greater than that of normal tissues including blood), the fact that carcinoma of the stomach is so often accompanied by absence of free hydrochloric acid, makes it "just the condition most favorable for a continuance of the salivary action"; then in concluding says: "In view of these facts the glycytryptophan test is of no value in the diagnosis of cancer" (!) Koehlker, working from a theoretical standpoint with other di- and tripeptids whose splitting he detects with the polariscope, finds that all

are hydrolyzed by saliva under experimental conditions similar to those used in Warfield's work. He is conservative in ascribing these effects to non-bacterial enzymes, but in view of the universal presence of ereptases in the tissues is inclined to the view that the peptid-splitting power of saliva is inherent.

In a second article Weinstein states that saliva is incapable of splitting Witte peptone. (As demonstrable by the bromin test for tryptophan.) Sanders and Rosenbloom disagree with this observation. From our own results it would appear that saliva as obtained from the mouth and protected with toluene frequently splits Witte peptone sufficiently to cause a marked increase in the formol-titrable nitrogen. Within twenty-four hours of incubation, however, we have not so far encountered positive tryptophan reactions. As regards the use of the glycytryptophan test for cancer diagnosis, Sanders and Rosenbloom endorse the position taken by Warfield, that it is worthless.

II.

Having now presented the salient features of the literature, certain general observations may be made.

The principle that carcinoma tissue contains an enzyme capable of splitting polypeptids and in greater strength than is found in normal tissue, blood and non-malignant new growths, has not been disputed. All agree that in a large majority of the cases of gastric carcinoma, the stomach contents show the power to hydrolyze polypeptids. So far the possibility of devising a suitable procedure for detecting the cancer enzyme for diagnostic purposes would seem as great as it ever was. But the practical application of the glycytryptophan procedure for this purpose has yielded inconstant results in the hands of different workers; some normal cases, many cases with low acidity and a few other non-malignant conditions, have reacted positively; some cases of definite carcinoma have reacted negatively. Although some writers, expecting too much from an organic chemical reaction, have gone too far in depreciation of the test, it must be conceded that the greatest indefiniteness in results has been observed among the very group of cases in which the suspicion of carcinoma is justified by already existing methods, and among which differentiation is most to be desired. A non-malignant case with low acidity is likely to react positively; an early carcinoma developing on an ulcer base with high acidity is likely to be negative.

In deciding just how valuable the test is it makes a great deal of difference how we explain these variations, the variations which occur in spite of precautions such as Neubauer and Fischer recommend. If reflux of pancreatic juice into the stomach without the presence of readily detectable bile is a frequent phenomenon, as held by Kuttner and Pulvermacher in accordance with the view of Boldeyreff and others, then the

test loses much of its value and no change in the details of its application will be likely to restore it. The pathologic-physiologic basis will have been undermined. If, as the work of Warfield and Koehlker appears to indicate, saliva possesses an enzyme which hydrolyzes polypeptids, the test in its present form falls to the level of a mere index of conditions in the stomach favorable for continuance of salivary digestion. Conceivably some means might be developed for eliminating these sources of error by controlling the reactions of the stomach contents or otherwise, but this is problematical. If, on the other hand, inconsistencies in the test are due to imperfections in the details of the method of applying principles which are correct, one might hope to eliminate the objectionable features.

Concerning the two most serious criticisms, that of Kuttner and Pulvermacher and that of Warfield, it is interesting to note that they are in part opposed to one another. One explains positive reactions in cases with low acidity by entrance of saliva through the cardia, the other by entrance of pancreatic juice through the pylorus. Both cannot be entirely right. If the reactions seen are due solely to saliva they are not due to pancreatic juice, and *vice versa*. The only ground for agreement would be the compromise that both processes are concerned.

Now there is no doubt that saliva as obtained from the mouth does in many cases contain something which has the power to cleave polypeptids. We have repeatedly confirmed this observation with glycyltryptophan and with Witte peptone.* It is equally certain that saliva passes normally into the stomach. Then given conditions in the stomach favorable for a continuance of this action and it follows that peptid splitting must occur there for this reason alone. In view of this consideration it is clear that the mere demonstration of polypeptid splitting power in gastric juice carries with it no proof of any second enzyme entering from the pylorus. Unless there are other proofs that pancreatic juice may gain access to the stomach than the mere detection of peptid splitting, or until such splitting is observed under conditions which preclude the effect associated with saliva, one is not warranted in the assumption that any reflux of pancreatic juice actually occurs. For the combined effects of pepsin and saliva are equal to the effect of trypsin. Boldyreff, Kuttner and Pulvermacher and others, have never excluded this source of error and the burden of proof lies with them.

Let us now consider more in detail the question of saliva. If pure sterile saliva contains an enzyme which can split peptids, the test has a limited value. If the observed splitting is due to bacteria, it is less serious obstacle. We have tested the action of saliva before and after passage through a Berkefeld candle and *have never seen any peptid splitting power in the filtered secretion, although it was frequently observed in the unfiltered samples*, and again in the filtered, after these

*In some samples of saliva, however, we have failed to demonstrate any peptid-splitting power.

had been inoculated with a mere loopful of the former. The process of filtration did not impair the amylolytic power of the saliva and we feel safe in the assertion that *non-filterable bodies in the saliva are responsible for its apparent peptid splitting action*. These non-filterable bodies are here regarded as bacteria, although some have suggested the possibility of a selective filtration of enzymes. Theoretically it would make no essential difference as to the effects which are seen in the stomach contents whether the action were bacterial or due to a secreted enzyme. The same chemical conditions might favor either, and on the other hand, high acidities, whether due to HCl or to an unusual quantity of lactic acid, would check bacteria as well as the enzyme. Warfield's results might be interpreted in this way as well as in another. All are familiar with the inhibition of the growth of certain bacteria in milk or in the bowel by the predominance of lactic acid bacilli and their product. Practically it is certain that whatever gives saliva its peptolytic power this can be effectually eliminated by mechanical means. Toluene is not free from objections.

Since heretofore no greater precautions have been taken in the study of peptolysis in stomach contents than in saliva, it is obvious that unless the conditions in the stomach are such as to check bacterial action already begun the same remarks apply here as have just been made for saliva concerning the chances of confusing bacterial action with that of native enzymes. Especially when there are infected teeth, gums or tonsils, and catarrhal processes in the nasopharynx or ragged ulceration in the gastric mucosa itself, will the chances for bacterial action be great. The experiments made by Neubauer and Fischer to determine how much attention should be paid to bacteria did not exclude the possibility that a heterogeneous mass of organisms in such culture media as may occur in subacid stomach contents, may actively split peptone. Nor is the simple filtration through paper, which they recommend, a reliable safeguard against this source of error. Papers vary; some are fairly effective, others not.

Up to this point, then, we find no basic objection to their test, but see in the inadequate provisions for excluding bacteria one explanation for disagreement among different observers. There are also other points to be considered. When gastric juice is mixed with a solution of glycytryptophan and the cleavage of the latter is detected by application of a bromin test, we end with a delicate and easily-masked color reaction, a purely qualitative test permitting scarcely a guess as to the extent of the splitting. Even then we are dealing solely with *the cleavage of a single dipeptid*. A given stomach content might cleave other peptids in greater quantity in one case, less in another. The substitution of Witte peptone or silk peptone for glycytryptophan introduces a theoretical difference even though in the end we gauge the cleavage by testing qualitatively for a single end-product. If we use Witte peptone and rely on the bromin test as an index of its splitting, we fail to observe any

cleavages except those which in the end liberate free tryptophan; hence considerable hydrolysis of this substance can occur before a positive bromin test is obtainable. The same applies to the use of silk peptone and observance of the tyrosin precipitate. On the other hand, a positive test implies a whole succession of hydrolyses which have carried the peptone down to its simplest components. For this very reason peptone may be a more suitable substance to use for clinical purposes. Theoretically glycyltryptophan should be a more delicate reagent than peptone under these conditions, because it cannot split at all without giving the substance (tryptophan) used as the index. Possibly it is too delicate for clinical purposes.

The greatest consistency in results might be expected from a quantitative method which would tell us the total peptid splitting power of a given gastric juice, acting under definite conditions for a definite time on a uniform mixture of polypeptids. Such a test should give us a set of figures from which to draw conclusions as to the amount of splitting which is to be regarded as normal, what the limits for the normal are, how much splitting power a positive qualitative tryptophan test corresponds to, how much splitting can occur in the non-malignant diseases, how much in cancer, etc. Such relative figures based on a series of observations naturally would not be regarded as absolute, but they should enable us to classify stomach contents on the basis of polypeptid splitting power in the same way that we now compare them on the basis of acidity.

For this purpose we have used a 2 per cent. aqueous solution of Witte peptone which is mixed with gastric juice and subjected to formol titration in accordance with the method of Ronchése-Malfatti-Sörenson. After titration of a 10-c.c. sample of the mixture the remainder is placed in the incubator and after twenty-four hours retitrated. The excess of peptone by combining any free acid which may be present makes further neutralization unnecessary.

In applying this method in a series of cases, we have aimed especially to ascertain (1) whether normal gastric juice and saliva split peptone at all, and, if so, to what extent; (2) how much of the peptid-splitting power which has been observed in saliva, and in gastric juice of non-malignant diseases, is due to bacteria; and whether, if the action of bacteria is certainly excluded, there still remains in such gastric juices any splitting power which would have to be ascribed to reflux of pancreatic juice unaccompanied by bile; (3) how much of the peptid splitting seen in cancer cases is due to bacteria and how much is due to other causes (e. g., cancer enzyme); (4) the value in diagnosis of the quantitative method as compared to that of simply testing for tryptophan in the Witte peptone, gastric juice mixtures after incubation, and in general the

diagnostic value of any method for detecting polypeptid or peptid splitting power in gastric juice.¹

III.

The results obtained may be summarized as follows:

Saliva as obtained from the mouth, filtered simply through paper and incubated under toluene, often but not always has the power to split Witte peptone and glycyltryptophan. But if the saliva is filtered through a Berkefeld candle and kept aseptic, all detectable peptolysis disappears. The same is true for its power to split glycyltryptophan. If the aseptic peptone-saliva mixture be inoculated with a drop of unfiltered saliva, peptolysis again occurs (Table 1).

The peptolytic power of gastric juice (and blood) has been estimated in terms representing the increase in the number of c.c. of N10 KOH required in the formol titration of 100 c.c. gastric juice (or serum) with 200 c.c. 2 per cent. Witte peptone solution after twenty-four hours incubation at body temperature. This figure, here designated as the *peptolytic index*, is used for comparisons.

The peptolytic index for pure, fresh blood-serum from healthy individuals was found to average 8, part of the rise being due to autolysis of the serum itself.

For normal gastric juice as studied in forty cases, the minimum was 0, maximum 18, average 10.5, or about that found for serum. In none of the forty cases was there a positive color test for tryptophan before or after incubation with peptone solution (Table 2).

In ten cases of hyperacidity the minimum index was 0, maximum 6, average .6 (lower than the normal). (Table 3.)

In twenty-two cases of subacidity and anacidity in which the free HCl ran from 10 to 0, total acidity 20 to 5, the maximum peptolytic index was 33; minimum .0, average 9 (Tables 4 and 5).

The indices, then, were lowest in hyperacidity, a little higher in the normal, a little higher yet in some of the stomach contents from cases of an- and subacidity. For this entire group of seventy-six normal and non-malignant cases the inverse relationship between acidity and pepto-

1. We had intended also to compare the results obtained by the Neubauer and Fischer method with those obtained by simple substitution of Witte peptone for glycyltryptophan, and those of the quantitative method herein described. But at the time this work was begun (some two years ago), we had trouble in obtaining "*ferment diagnosticum*." We regret, therefore, our inability to state whether in a long series of cases substitution of Witte peptone for the dipeptid is more or less advantageous, except by comparing our results with the published results of others. Such comparison suggests that Witte peptone is less likely to yield a positive result in non-malignant conditions and equally reliable in cancer cases. Perhaps glycyltryptophan, for reasons already mentioned, is too sensitive. The peptone is also cheaper.

lysis as observed for glycytryptophan by Warfield, seems to hold good. Tryptophan reactions were, however, uniformly negative.

One case of non-malignant stenosis gave a positive tryptophan reaction with bromin. In this instance stomach contents were examined on three different days. The indices ran .0, 7 and 9, average 5.3, or well within the normal limits. This shows the possibility of encountering now and then a positive color reaction with what may be regarded as a "normal" peptolytic power. It explains possibly some of the discrepancies in results obtained by qualitative methods. Since theoretically "*ferment diagnosticum*" should show free tryptophan to the bromin test with a slighter peptid splitting power than with peptone, for reasons already given (p. 566) it may well be that this dipeptid is even more likely than peptone to give a positive result with a normal case.

Four of the samples in the subacidity series which showed the highest peptolysis were filtered through a Berkefeld filter and mixed with peptone solution under aseptic conditions. In cases so treated the index always became 0. (Table 5, Cases 113, 114, 115, 117.) This observation, together with the point previously mentioned, that in non-malignant cases peptolysis and acidity are in an inverse relationship, indicates that in these benign cases, peptolysis is due to bacteria whose action is inhibited by acid.

Twenty-three cases of cancer have been studied from which thirty-three samples of gastric juice were obtained (Tables 6 and 7). In all cases the diagnosis was made at operation or at autopsy. Six of the malignant series were cases of carcinoma developing on an ulcer base, with free HCl between 15 and 20, total acidity 60 to 70 (Table 6, last six cases). In this group, in spite of acidities above those of the non-malignant cases, the indices ran, maximum 72, minimum 48, average 69; i. e., the minimum index is once and a half that of the maximum found in forty normal and thirty-six non-malignant subacidity cases. The tryptophan reaction after incubation with Witte peptone was positive in all. These findings do not confirm the views of Warfield that peptolysis is due to a salivary enzyme which fails to act when the acidity is high. Twelve of the fourteen cancer cases with free HCl 0, and total acidity between 5 and 10 (Table 7), gave indices as follows: maximum 165, minimum 63, average 98.5; i. e., the least index was twice as great as the maximum non-malignant figure encountered, while the maximum was five times as great. The average was nearly ten times that of the normal average (10.5).

The qualitative tryptophan test was positive in thirteen of the fourteen, and failed in one case (Case 75) in spite of the low acidity and the excessive peptolysis shown by titration. Two of the fourteen cancer cases

(Table 7, Cases 60 and 86) gave indices not so greatly exceeding the highest non-malignant figures.

In four cases doubt had existed as to the diagnosis. In each of these the free HCl and total acidity were 5 and 15, respectively (by coincidence). The peptolytic indices by the antiseptic method averaged 148; minimum 120, maximum 165. The tests in this series were also made by the aseptic method (filtration through a Berkefeld candle and subsequent use of sterile pipettes and flasks without toluene). The indices then averaged 97.5, maximum 105, minimum 87. Peptolysis was reduced by the filtering, but only moderately so and remained on the average nearly ten times as high as the normal average, even when for the latter we take the figures of the toluene method. Exploratory operation was made and revealed carcinoma in each case (Cases 99, 112, 120, 122; Table 7).

TABLE 1.—TESTS WITH SALIVA

Saliva, 1 part; sterile peptone solution, 2 parts. Of the mixture 10 c.c. subjected at once to formol titration; a second 10 c.c. incubated for twenty-four hours with addition of acid or alkali as indicated under remarks. *A* indicates that toluene was used for antiseptics; *B*, that the saliva was filtered through a Berkefeld filter and handled aseptically. The table shows comparative effects of toluene and filtration; also the high peptolysis when neither is used.

— Formol Titration —

No. of Exper.	Before Incuba- tion	After Incuba- tion	Rise	Br. Test	Remarks
I	1.5	2.0	0.5	0	A. No addition of acid or alk.
II	1.1	2.1	1.0	0	A. Made alkaline to litmus.
III	1.0	1.3	0.3	0	A. Made alk. to phenolphthalein.
IVa	0.9	1.1	0.2	0	A. Added N/10 to make .18%.
IVb	0.9	1.1	0.2	0	A. Added N/10 to make .36%.
IVc	0.9	1.0	0.1	0	A. Added N/10 HCl to make .18%.
Va	1.1	1.3	0.2	0	A. No addition.
Vb	1.1	7.2	6.1	0	Same with toluene omitted.
Vc	1.1	1.1	0.0	0	B. No addition.
VI	1.4	1.4	0.0	0	B. No addition.
VIb	1.4	2.5	1.1	0	Same reinfection with fresh saliva.
VII	4.5	4.5	0.0	0	B. No addition.

In one case the contents were obtained at autopsy. By the usual method of examination with filtration through paper and incubation under toluene, the index was 186; with no toluene added it was 219; after filtration through porcelain without using toluene, 129, showing the inhibiting effect of toluene to be less than that of filtration. The figures obtained in the last five cases cited also show that neither filtration nor toluene, nor a combination of the two will eliminate the peptolytic power from certain cancerous stomach contents, from which it is apparent that, unlike what was found for benign and normal conditions, we have to do in cancer cases with two peptolytic fractions, viz., microorganisms and something filterable. The filterable peptolyzing agent might be regarded as an extracellular enzyme from bacteria or a ferment from cancer. Saliva and normal gastric juice and that from subacidity cases, however,

TABLE 2.—TESTS WITH GASTRIC JUICE—NORMAL CASES

Table made from the data obtained in forty cases. No symptoms in any. Free HCl, 30-40. Total acidity, 50-60 in all. Bile, blood and lactic acid tests negative in all. Table includes the extremes and averages of 40 cases.

Case	— Formol Titration —			Test	Acidity		Remarks
	Before Incuba- tion	After Incuba- tion	Rise		HCl	Total	
65	.6	1.2	.6	0	30	58	Case which showed greatest peptolysis.
121	.5	.5	0	0	39	56	
63	.8	.8	0	0	40	58	Two characteristic cases with no demonstrable peptolysis.
Av.	.6	.95	.35	0	35	55	

Peptolytic index: Max. 18; Min. 0; Av. 10.5.

TABLE 3.—TESTS WITH GASTRIC JUICE—HYPERACIDITY CASES

Ten cases, with HCl 50-80; total acidity 70-110. Bile, blood and lactic acid always absent and no sign of dilatation or obstruction. Symptoms such as occur commonly in "hyperchlorhydria" with nothing to suggest, directly, ulcer or other organic stomach disease; (or, no symptoms, the hyperacidity having been discovered by routine).

Case No.	— Formol Titration —			Test	Acidity		Remarks
	Before Incuba- tion	After Incuba- tion	Rise		HCl	Total	
3	.3	.3	0	0	60	70	Epileptic.
14	.2	.2	0	0	60	75	
21	.2	.2	0	0	65	90	
32	.2	.2	0	0	70	98	
44	1.2	1.2	0	0	50	70	
46	1.2	1.4	.2	0	81	109	Morning aspiration.
48	1.0	1.0	0	0	56	76	
50	1.6	1.6	0	0	69	85	
41	1.5	1.5	0	0	63	111	
52	.6	.6	0	0	72	86	

Peptolytic index: Max. 6.0; Min. 0; Av. .6.

TABLE 4.—TESTS WITH GASTRIC JUICE—SUBACIDITY CASES, A

Ten cases with free HCl 10-15; total acidity 25-30. Bile, blood and lactic acid tests uniformly negative.

Case No.	— Formol Titration —			Test	Acidity		Remarks
	Before Incuba- tion	After Incuba- tion	Rise		HCl	Total	
23	.8	.8	0	0	12	25	Symptoms in these cases were mild, e. g., anorexia, weight or distress p. e. with headache and neurasthenic symptoms. Physical findings were negative; no ptoses, no dilatations, no motor inefficiencies. In three cases diarrhea was present.
24	1.5	1.5	0	0	8	15	
25	1.0	1.2	.2	0	10	20	
51	1.0	1.3	.3	0	10	26	
53	.4	.7	.3	0	10	30	
64	.9	1.2	.4	0	5	12	
88	1.3	1.3	0	0	10	26	
100	.7	1.0	.3	0	12	15	
104	.7	1.0	.3	0	10	25	
54	.9	1.5	.6	0	6	24	

Peptolytic index: Max. 18; Min. 0; Av. 7.2.

completely lose their peptolytic power with suitable filtration, from which it would appear that filtration is adequate for eliminating bacterial action. Others have shown that cancer tissues, aseptically prepared, do contain a peptolytic enzyme. Therefore it seems more plausible to ascribe the filterable agent to the cancer. Our own work, however, does not finally establish this point. Possibly a cancerous mucosa lodges bacteria which do not thrive under other conditions.

TABLE 5.—TESTS WITH GASTRIC JUICE—SUBACIDITY CASES B

Sixteen cases. Free HCl, 0; total acidity 8 to 30. In four of these cases (113, 114, 115, 117) filtration was carried out through a Berkefeld filter with subsequent aseptic handling, and also by the usual paper filtration with subsequent antiseptic (toluene) treatment.

Case No.	Formol Titration			Br. Test	Acidity		Lactic	Bile	Blood	Remarks
	Before Incuba- tion	After Incuba- tion	Rise		HCl	Total				
49	.9	1.2	.3	0	0	8	..	0	0	Filtered through paper toluene added.
62	1.5	1.7	.2	0	0	10	..	0	0	Same as above.
68	1.6	1.8	.2	0	0	10	0	0	0	Same as above.
70	.6	1.3	.7	0	0	12	0	0	0	Same as above.
73	.8	1.2	.4	0	0	6	0	0	0	Same as above.
95	1.2	1.6	.4	0	0	10	..	0	0	Same as above.
106	1.2	1.4	.2	0	0	30	0	0	0	Same as above.
109	.5	.8	.3	0	0	30	0	0	0	Same as above.
116	1.5	1.5	0	0	0	10	0	0	0	Same as above.
111	1.6	1.7	.1	0	0	12	0	0	0	Same as above.
66	.6	.9	.3	0	0	8	0	0	0	Same as above.
71	.7	1.8	1.1	0	0	22	0	0	0	Same as above.
113	.2	.4	.2	0	0	10	0	0	0	Same as above.
113	.2	.2	0	(Aseptic)
114	1.5	1.7	.2	0	0	10	0	0	0	Same as above.
114	1.5	1.5	0	(Aseptic)
115	.6	1.1	.5	0	0	12	0	0	0	Same as above.
115	.6	.6	0	(Aseptic)
117	1.2	2.1	.9	0	0	10	0	0	0	Same as above.
117	1.2	1.2	.0	(Aseptic)

Peptolytic index: Max. 33; Min. 0; Av. 10.5; 16 cases (usual method).

Peptolytic index: Max. 0; Min. 0; Av. 0; 4 cases (aseptic method).

Three cases of carcinoma showed indices of 0, 6 and 12, no higher than the benign series, and hence negative (Table 6; Cases 33, 87, 92). In one of these cases there was the high lactic acid content which Warfield found associated with negative glycytryptophan reactions; in the others the acidities were low. In all, 88 per cent. of the cancer cases were positive by the quantitative method, 83 per cent. by the qualitative. Of seventy-six non-malignant cases, only one gave a positive tryptophan test.

In the series of cases here reported, the maximum index found in any of seventy-six benign cases by the toluene method was thirty-three, and this was seen in but one case. The minimum index in the cancer cases, barring three, was forty-five. For practical purposes we may say then that when reliance is placed on paper filtration and toluene

Indices of 0-20 are negative.

Indices of 20-40 are suspicious.

Indices of 40 and over are positive.

TABLE 6.—MALIGNANT CASES

Nine cases of carcinoma with free HCl, 0 to 20; total acidity, 5 to 70. Diagnosis confirmed in all but two obvious cases either at operation or at autopsy.

Case No.	Formol Titration			Br. Test	Acidity			Blood	Lactic	Remarks
	First	Second	Rise		HCl	Total	Bile			
33	1.2	1.4	.2	0	0	6	0	0	++	Negative Cases: All were operated on. Cases 33 and 92 showed cancer at lesser curvature; Case 87 cancer at pylorus. Note low acidity in two cases.
87	1.2	1.2	.0	0	0	36	0	0	++	
92	1.5	1.9	.4	0	0	5	0	0	0	
118	*A.M. 1.7	4.0	2.3	+	10	30	0	0	0	Six cases of malignant disease with high total acidities; carcinoma of pylorus found at operation in each case. Marked rise in every case in spite of acidity.
	2.0	4.4	2.4		8	21	0	0	0	
37	A.M. 2.1	4.6	2.5	+	15	70	0	0	0	
	1.6	4.0	2.4		18	60	0	0	0	
61	A.M. 1.4	3.8	2.4	+	20	70	0	0	0	
	1.4	3.7	2.3		15	65	0	0	0	
81	A.M. 1.3	4.1	2.3	+	10	70	0	0	0	
	1.7	4.3	2.6		12	60	0	0	0	
82	A.M. 1.6	3.9	2.3	+	6	53	0	0	0	
	2.0	4.1	2.1		15	63	0	0	0	
83	A.M. 1.3	2.9	1.6	+	8	60	0	0	..	Peptolytic Index: Av. 69; Max. 72; Min. 48.
	1.4	3.8	2.4		15	60	0	0	0	

* A.M. = Material aspirated in morning before giving test breakfast.

There is no doubt that the significance of demonstrable peptolysis of even moderate degree, if observed in aseptic specimens, is much greater than that seen when it is necessary to allow leeway for bacteria and establish empiric borders. From the series of ten non-malignant cases in which we have filtered gastric juice through a Berkefeld filter all peptolysis has disappeared, and it is anticipated further work will show that any peptolysis which survives filtration of this sort is abnormal and likely to mean cancer, provided always that gastric juices containing bile be excluded. For accurate work the aseptic method should be used exclusively. It will be found most practical, perhaps, for ordinary clinical purposes, to dispense with filtration in cases with very low and very high indices and apply it in case of uncertainty: i. e., when the figures are between 20 and 40.

It is also important to exclude bacteria when using the qualitative test, since those present in non-malignant cases will sometimes cause a positive reaction. It is possible also that an overgrowth of certain forms, such for instance as lactic acid bacilli, may be responsible for a negative result in a cancer case.

TABLE 7.—MALIGNANT CASES

Fourteen cases of carcinoma with free HCl, 0 to 20; total acidity, 5 to 70. Diagnosis confirmed in all but two obvious cases either at operation or at autopsy.

Case No.	Formol Titration			Br. Test	Acidity			Blood	Lactic	Remarks
	First	Second	Rise		HCl	Total	Bile			
86	2.2	4.0	1.8	+	0	5	0	0	+	Clinical diagnosis — cancer — confirmed at operation.
93	2.1	4.2	2.1	+	0	5	0	0	+	Obvious mass, metastases, cachexia, death; no autopsy.
101	2.2	4.6	2.4	+	0	5	0	0	+	Clinical diagnosis of cancer confirmed at operation.
102	2.2	4.4	2.2	+	0	5	0	0	+	Clinical diagnosis of cancer confirmed at operation.
37	2.2	4.5	2.3	+	0	5	0	0	+	Clinical diagnosis of cancer confirmed at autopsy.
58	2.4	4.6	2.4	+	0	5	0	0	0	Clinical diagnosis of cancer confirmed at autopsy.
60	2.2	3.7	1.5	+	0	10	0	0	0	Clinical diagnosis of cancer confirmed at autopsy.
75	2.1	5.1	3.0	0	0	10	0	0	0	Clinical diagnosis of cancer confirmed at autopsy.
76	2.2	5.2	3.0	+	0	10	0	0	0	Epigastric tumor, nodular liver, cachexia, no autopsy.
84	1.9	4.0	2.1	+	0	8	0	0	?	Clinical diagnosis of cancer confirmed at autopsy.
99	1.5	7.0	5.5	+	0	5	0	0	+	Clinical diagnosis, "suspicious": carcinoma at operation.
99†	1.5	5.0	3.5	+						
112	1.5	7.0	5.5	+	0	10	0	0	+	Clinical diagnosis, doubtful; operation — death, autopsy; carcinoma.
112†	1.5	4.4	2.9	+						
120	1.5	5.5	4.0	+	0	5	0	0	+	Clinical diagnosis doubtful. Operation showed posterior wall carcinoma with glandular and hepatic metastases.
120†	1.5	4.8	3.3	+						
122	1.3	6.2	4.9	+	0	6	0	0	+	Clinical diagnosis of cancer confirmed at autopsy.
122†	1.3	4.3	3.0	+						

† Aseptic method.

Peptolytic index, antiseptic (toluene) method: Max. 165; Min. 45; Av. 105.

CONCLUSIONS

1. Saliva free from bacteria does not split Witte peptone nor glycylotryptophan.

2. Normal gastric juice free from blood, bile (trypsin) and bacteria has no peptolytic power. The same holds true for cases of benign subacidity.

3. Peptolytic and peptidolytic action exhibited by saliva, and so-called "tryptic" digestion in the stomach when there is no bile to indicate reflux of intestinal contents, are usually due to unfilterable agents (bacteria).

4. There is no incontestable evidence to show that pancreatic juice unaccompanied by bile ever gains access to the stomach (except in cases with acholic intestinal contents).

5. Toluene is inadequate for the exclusion of bacterial action in experiments with saliva and gastric juice.

6. In about 88 per cent. of developed cases, carcinomatous stomach contents show a peptolytic power two to ten times the maximum seen in benign conditions in general. This is due in part to bacteria, but high peptolysis persists after filtration through a Berkefeld and subsequent aseptic handling.

7. Witte peptone may be advantageously substituted for "*ferment diagnosticum*" in the Neubauer and Fischer qualitative test, with results in malignant cases as good as any that have been published for glycyl-tryptophan itself. In non-malignant cases it has been positive but once in seventy-six normal and *Subacid* cases.

8. The quantitative method herein described yields slightly more uniform results than the qualitative procedure in cancer cases. It has never been found "positive" in seventy-six normal and non-malignant cases.

9. The detection or measurement of peptolytic power in gastric juice, if carried out by any suitable method, is of considerable value in the diagnosis of cancer.

10. It is of value in any case, and essential in doubtful cases, to eliminate bacteria by passage of the gastric juice through a Berkefeld or other equally effective filter, with subsequent aseptic precautions.

IV.—EXPERIMENTAL

MATERIAL

Saliva was obtained from different members of the laboratory staff. The mouth was rinsed with water and the flow promoted by masticating a bit of paraffin. Samples from different individuals were used in some experiments, mixtures in others. The material was filtered through paper or through a Berkefeld candle as indicated on the charts.

Stomach contents were obtained by aspiration one hour after a test breakfast consisting of 30 gm. bread and 200 c.c. water. In most instances the stomach was emptied in the morning prior to giving the test breakfast, and the results of both aspirations examined. Unless specified on the charts as "morning aspiration" the material is understood to have been obtained after a test breakfast. In one case the material was obtained at autopsy. Each sample was subjected to a test for bile (dilute alcoholic iodine), for blood (Weber), lactic acid (Uffelmann), and the usual routine titrations, with demethyl-amido-azo-benzol and phenolphthalein. A direct test for tryptophan with dilute bromine water or bromine vapor was also made. Samples giving positive bile or blood reactions, or having a yellow or greenish color even in the absence of positive tests, were not used. The material was filtered through a folded filter or a Berkefeld candle, or both, as indicated in the records.

Cases were drawn from the Cook County and Presbyterian hospitals, Chicago, the dispensary of Rush Medical College, the private practice of Dr. Jacque and scattering sources. It has been necessary in some malignant cases to rely on the word of the operating surgeon for the final diagnosis, without histological examination. Cases of this sort which have been included have been operated on by surgeons of known competence. For help in obtaining cases, records and material, we are especially indebted to Dr. Donald Abbott, interne in Cook County Hospital. We also desire to acknowledge the support of Dr. Frank Billings, Dr. James B. Herriek, Dr. A. D. Bevan, Dr. J. Davis and others, for use of material.

METHODS

Peptone Solution.—A 2 per cent. solution of Witte peptone is filtered through a folded filter, distributed in 60 c.c. flasks, sterilized in an autoclave and kept on ice. If the flasks are both cotton- and cork-plugged, the stock solution keeps its titer for a long time. One flask is used for each set of experiments.

PROCEDURE

A. (Antiseptic). Ten c.c. gastric juice (filtered through a folded filter) are measured into a flask by means of a pipet. To this are added exactly 20 c.c. peptone solution and, after mixing, a layer of toluene is added. Exactly 10 c.c. of the mixture are withdrawn from under the toluene with a pipet and subjected to formol titration as follows: To the 10 c.c. of mixture add 50 c.c. H_2O and 5 drops of 1 per cent. alcoholic phenolphthalein, then N/10 KOH to the first permanent pink tint. Take 5 c.c. liquor formaldehydi diluted with 10 c.c. water, add 5 drops phenolphthalein and neutralize in the same way. Add the neutral formol solution to the neutral peptone gastric juice mixture. The mixture becomes acid. Titrate back to the first permanent pink and note the number of tenth cubic centimeters required.²

2. *Note.*—In using phenolphthalein as indicator and bringing to the first permanent pink both for the original neutralization and in the final titration, we intentionally disregard the criticism that for absolute values neutralization with litmus and a final titration to violet with phenolphthalein is preferable. These figures are purely relative and the use of phenolphthalein as proposed by Malfatti for the urinary NH_3 is quicker and more satisfactory for this purpose.

The remaining 20 c.c. of peptone gastric juice solution (a) are placed in the incubator for twenty-four hours (stoppered) and at the end of this time 10 c.c. are withdrawn and treated as before. The first titration figure is subtracted from the second and the difference is an expression of the peptolysis which has occurred in a mixture of $3\frac{1}{2}$ c.c. gastric juice with $6\frac{2}{3}$ c.c. peptone solution ("Rise"). The rise multiplied by 3 and by 10 gives the figures for peptolysis in 100 c.c. gastric juice with 200 c.c. Witte peptone solution ("Peptolytic Index.") When sufficient material is available it is preferable to use double quantities of gastric juice and peptone solution for the titrations.

B. (Aseptic) The gastric juice is passed through a sterilized kaolin filter (Berkefeld) and subsequently handled in sterile pipets and flasks which are plugged with both cotton and cork. No toluene is used.

The qualitative test is performed by simply adding cautiously to 5 c.c. of the solution to be tested a drop or two of dilute bromin water and observing the delicate rose or rose-violet tint which occurs in presence of tryptophan.

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THE RELATION OF THE VIRULENCE OF THE TUBERCLE BACILLUS TO ITS PERSISTENCE IN THE CIRCULATION *

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Bacteria frequently gain access to the circulation. However, there is still a marked difference of opinion as to how frequently this occurs and how serious this invasion is, some believing that it is a phenomenon always accompanied by marked systemic disturbance, others that if the number of bacteria is small, the body rids itself of the invaders without the aid of any general reaction. It is known that microorganisms are eliminated from the circulation chiefly by way of the kidneys and of the liver, but it is not known what the determining factors are. Are the bacteria filtered from the blood stream by means of the tissues, in the same way as inert foreign particles; for example, as would be the case if an equal amount of egg white had found its way into the blood, or does this mechanical process play a rôle secondary to other finer defensive processes?

The following investigation was undertaken primarily to obtain some answer to a simple question, to discover whether, quite independently of their power of multiplication, a direct relationship exists between the virulence of bacteria and their ability to maintain an existence in the circulation. It seemed as if the tubercle bacillus presented an unusual opportunity for a study of this nature. For, as is well known, the bovine type of tubercle bacillus is highly virulent for rabbits when a small fraction of a milligram is injected intravenously, whereas the human type of this bacillus is but slightly virulent, possessing the power of giving rise to merely local lesions in the lungs and in the kidneys, which do not disseminate the disease or result in the death of the animal. The two types of bacilli are almost alike morphologically, and multiply so slowly as to make this factor negligible in an experiment of short duration. Their chief and preeminent difference is that of virulence. A series of tests was therefore instituted, which, briefly stated, consisted in inoculating a measured quantity of human and of bovine tubercle bacilli into the circulation of rabbits, and of determining whether they persisted in the blood-stream for approximately the same length of time.

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The experiments were planned as follows: Four rabbits were injected for each test, two with a human type of bacillus, the other two with the bovine type; in each case .01 mg. and 1 mg. of a culture was suspended in a salt solution and injected into the ear vein. These four animals, which were of about equal weight, were bled at regular intervals, generally one-half hour, one hour, two hours and three hours after inoculation, 5 c.c. of blood being caught in a solution of sodium citrate. Thus there were eight specimens taken from the two rabbits inoculated with the human tubercle bacillus, and eight from the two inoculated with the bovine bacillus. These sixteen specimens of blood were immediately injected subcutaneously into as many guinea-pigs, and after six weeks these animals were examined for tuberculosis.

In addition to a series of experiments of this description, others were undertaken in which the rabbits were bled soon after inoculation, or after a period longer than three hours following the injection of the bacteria. Furthermore, it was possible to test the blood of a large number of rabbits which, in the course of various laboratory work, had been inoculated with bovine or with human tubercle bacilli, and to study, in this connection, the relation of bacteremia to the tuberculous condition of the animal—a subject which in the field of human pathology has been the center of much discussion during the past few years, and which we touched on only incidentally.

It will be seen from the accompanying table (Table 1) that six experiments, of the type which has been outlined, were successfully carried out. Others were undertaken, but owing to difficulty in bleeding the rabbits, to occasional clotting of the blood, to the premature death of some of the guinea-pigs, or to other unavoidable causes, they had to be altogether rejected.

The table shows our results more clearly than mere description. If we take the first experiment, for example, we find that of the eight pigs inoculated with the blood of rabbits injected with bovine tubercle bacilli, four showed tuberculosis when killed after an interval of six weeks, one died prematurely, so that three of the eight tests were negative. On the other hand, only one specimen of the eight taken from the two rabbits inoculated with the human culture incited tuberculosis in the guinea-pigs used for the tests. In this way the experiments may be interpreted. Table 2 brings out these results more clearly, and is a summary of all six experiments. Here we see that there were forty-four rabbits inoculated with a culture of human tubercle bacilli, and an equal number of successful inoculations with bovine culture. This includes all specimens of blood drawn at intervals varying from one-half to three or four hours after the rabbits were inoculated. Of the bovine tests eighteen were found to contain tubercle bacilli, that is, 59

per cent., whereas of the tests with human culture only four gave rise to tuberculosis in the guinea-pigs; that is, only a little over 9 per cent. It will be seen that there is some irregularity in the results; that at times bacilli were found in the circulation after two or three hours, although they were not demonstrable after shorter intervals. The difference between the two groups as shown in this table is, however, so marked that the conclusion is definite that the two types of bacilli, the markedly virulent and the feebly virulent, differ decidedly in their

TABLE 1.—RELATIVE PERSISTENCE OF THE HUMAN AND THE BOVINE TUBERCLE BACILLUS IN THE CIRCULATION

EXPERIMENT I						
1	—	Tb.	—		
2	—	Tb.	Tb.		
3	0	Tb.	—		
4	Tb.	—	—		
EXPERIMENT II						
1/2	—	—	Tb.	—	
1	—	—	—	Bovine culture was almost avirulent for rabbits.	
2	—	—	—		0
3	—	—	—		—
EXPERIMENT III						
1/2	0	—	—	Suggests possible confusion between the two "bovine" rabbits.	
1	Tb.	0	—		—
2	Tb.	—	—		—
3	Tb.	—	—		Tb.
EXPERIMENT IV						
1/2	Tb.	Tb.	—	0	Clot interfered with fourth test of first column and third test of third column.
1 1/2	Tb.	Tb.	—	0	
2 1/4	Tb.	Tb.	—	0	
3 1/4	—	Tb.	—	—	
EXPERIMENT V						
1/2	Tb.	Tb.	—	—	
1	Tb.	Tb.	—	—	
2	Tb.	—	—	—	
3	—	Tb.	—	—	
EXPERIMENT VI						
1/2	0	Tb.	—	—	
1	Tb.	Tb.	—	—	
2	—	Tb.	Tb.	—	
3	Tb.	Tb.	—	—	

Tb. = Tuberculosis of guinea-pig; — = no tuberculosis; 0 = premature death, etc.; B. = Bovine; H. = Human.

ability to persist in the circulating blood. That this difference is intimately associated with virulence was further brought out by an experiment in which a bovine culture was used, which was almost avirulent for rabbits as the result of prolonged artificial cultivation. (Table 1, Exper. II.) In this experiment, the bovine bacilli were not found in the circulating blood in any instance. Furthermore, it must not be thought that the negative results of the various tests with the human culture

were attributable to its having lost its virulence for guinea-pigs, for a series of tests using from .001 mg. to .000000001 (1/1,000,000,000) mg. of culture proved that .00001 (1/100,000) mg. incited a marked tuberculosis when injected subcutaneously.

Table 3 is a record of bleedings of a rabbit made at various intervals for more than twenty-four hours after it was inoculated with 1 mg. of a virulent bovine culture. It will be seen that these bacilli were still circulating in the blood twenty-seven hours after inoculation. In tests instituted one week to two months after inoculation with a bovine

TABLE 2.—SUMMARY OF SIX EXPERIMENTS OF TABLE 1

Experiment	Bovine Tb.		Human Tb.	
1	4	3	1	7
2	0	8	1	6
3	3	3	1	7
4	7	1	0	5
5	6	2	0	8
6	6	1	1	7
	<hr/>		<hr/>	
	+	—	+	—
	26	18	4	40
	<hr/>		<hr/>	
Total No. of cases.....	44		44	
Tb. per cent.	59		9.1	

+ = rabbit's blood contained tubercle bacilli.

— = rabbit's blood did not contain tubercle bacilli.

TABLE 3.—PERSISTENCE OF BOVINE TUBERCLE BACILLI IN THE BLOOD
(27 HOUR TEST*)

Time of Bleeding	Interval after Inoculation, Hours	Guinea-pig Test	Time of Bleeding	Interval after Inoculation, Hours	Guinea-pig Test
2 p. m....	2	Tb. +	9 a. m....	21	Tb. +
3 p. m....	3	Tb. +	11 a. m....	23	Tb. +
4 p. m....	4	Tb. +	1 a. m....	25	Tb. +
5 p. m....	5	Tb. +	3 a. m....	27	Tb. +

* 1 mg. of bovine culture in 1 c.c. of salt solution was inoculated into a rabbit. Five c.c. of blood tested.

culture (Table 4 A), tubercle bacilli were found in six out of seventeen instances, and all six had been injected from one to two months previously. So that it would seem that there exists a period in which the blood is sterile, an intermediate period between the time when the bacilli originally inoculated are eradicated from the blood-stream, and when in the course of a progressive tuberculosis, bacilli once more gain access to the general circulation. Among twenty-three similar tests in which a culture of human tubercle bacilli was inoculated, producing, however, but slight or no tuberculous lesions, only two showed bacilli in the blood (Table 4 B). In one of these positive cases a careful post

mortem examination of the rabbit failed to reveal any tuberculous lesion; we regard the finding of bacilli in this instance as an interesting but chance occurrence.

TABLE 4.—LATER TESTS OF INOCULATED RABBITS
A. BOVINE

No. of Rabbit	Interval Since Inoculation Days	Amount of Blood Tested c.c	Autopsy of Rabbit	Result of Blood Test
1148	7	7	Tb.	Tb.
1149	7	7	Tb. (m.)	Neg.
1149	14	7	Tb. (m.)	Neg.
1149	16	7	Tb. (m.)	Neg.
1153	14	7	Tb. (m.)	Neg.
1153	22	6	Tb. (m.)	Neg.
1155	21	6	Tb.	Neg.
1155	29	6	Tb.	Neg.
1152	30	7	Tb.	Neg.
1100	30	4.5	Tb.	Tb.
1100	30	4.5	Tb.	Tb.
1127	30	...	Tb.	Tb.
1126	30	...	Tb.	Tb.
1126	42	5	Tb.	Neg.
1160	35	7	Tb.	Neg.
1159	60	10	Tb.	Tb.
1159	60	10	Tb.	Tb.

B. HUMAN

1158	1	5	.	Neg.
1109	17	3	Neg.	Neg.
1109	20	6	Neg.	Neg.
1110	17	3	Tb.*	Tb.
1110	20	6	Tb.*	Neg.
1110	60	...	Tb.*	Neg.
1105	17	3	Tb.*	Neg.
1105	20	6	Tb.*	Neg.
1104	17	3	Tb.*	Neg.
1104	24	6	Tb.*	Neg.
1107	17	3	Tb.*	Neg.
1107	24	6	Tb.*	Neg.
1103	17	3	Neg.	Neg.
1103	24	6	Neg.	Neg.
1108	17	3	Neg.	Neg.
1108	24	6	Neg.	Neg.
1118	30	5	Neg.	Tb.
1118	90	3.5	Neg.	Neg.
1118	90	10	Neg.	Neg.
1121	30	5	Neg.	Neg.
1121	90	3.5	Neg.	Neg.
1121	90	3.5	Neg.	Neg.
1161	30	7	Neg.	Neg.

m = Miliary tuberculosis. The other rabbits had typical, massive bovine tuberculosis.

* Slight.

It is difficult to form a satisfactory hypothesis to explain the mechanism by which bacteria are able to circulate hundreds of times within the blood-stream and persistently escape the tissue filters. The feebly virulent human type, as well as the bovine bacillus, was regularly found in the blood from three to twenty minutes after inoculation (Table 5).

TABLE 5.—EARLY BLEEDINGS OF INOCULATED RABBITS

Nature of Inoculation	Interval After Inoculation, Minutes	Amount of Blood Tested, c.c.	Result
Bovine (1 mg.).....	3	5	Tb. +
Bovine (1 mg.).....	10	5	Tb. +
Bovine (1 mg.).....	20	5	Tb. +
Human (1 mg.).....	3	5	Tb. +
Human (1 mg.).....	10	5	Tb. +
Human (1 mg.).....	20	5	Tb. +

TABLE 6.—ANAPHYLACTIC SYMPTOMS FOLLOWING SUBCUTANEOUS INJECTION OF RABBITS' BLOOD

Condition of Rabbit	Amount of Blood Injected, c.c.	Anaphyl-acti-c Symptoms	Death	Remarks *
Bovine Tb.	5	++	+	Died in ½ hr.
Bovine Tb.	5	—	..	
Bovine Tb.	5	++	+	
Bovine Tb.	5	++	..	
Bovine Tb.	5	++	..	
Bovine Tb.	5	++	..	
Bovine Tb.	5	++	+	Died in 1½ hrs.
Bovine Tb.	5	++	+	Died in 1½ hrs.
Bovine Tb.	5	+	..	
Bovine Tb.	5	+	..	
Bovine Tb.	5	—	..	
Bovine Tb.	3.5	++	..	
Bovine Tb.	5.5	+	..	Blood in refrigerator over night.
Bovine Tb.	7	++	+	Death in 28 hrs.
Bovine Tb.	7	++	+	Blood in refrigerator nine days.
Bovine Tb.	7	++	+	Blood in refrigerator nine days.
Bovine Tb.	10	++	..	
Bovine Tb.	14	++	..	
Human Tb.	5	—	..	Rabbits almost free from tubercu- lous lesions.
Human Tb.	5	—	..	Rabbits almost free from tubercu- lous lesions.
Human Tb.	5	—	..	Rabbits almost free from tubercu- lous lesions.
Human Tb.	5	—	..	Rabbits almost free from tubercu- lous lesions.
Human Tb.	5	—	..	Rabbits almost free from tubercu- lous lesions.
Human Tb.	7	++	..	Rabbits almost free from tubercu- lous lesions.
Human Tb.	7	+	..	Rabbits almost free from tubercu- lous lesions.
Normal	5	+	..	
Normal	5	—	..	
Normal	5	—	..	
Normal	5.5	—	..	
Normal	7	+	..	
Normal	7	+	..	
Normal	7	—	..	
Normal	7	—	..	
Normal	10	++	..	
Normal	10	—	..	
Normal	17.5	++	..	

* Guinea-pigs weighed about 250 gm

It is possible that the bacilli cling to the walls of the vessels and escape the current of the circulation for considerable periods. However, in view of the lack of experimental data in this particular it is best to forego hypotheses. This is likewise true in regard to efforts attempting to account for the difference in this respect between the virulent and the comparatively avirulent types of tubercle bacilli. It is not attributable, however, to a difference in the opsonic power of the blood; tests which we carried out, as well as those of others,¹ show that no clear distinction exists between the indices for the human and for the bovine types of tubercle bacilli.

In the course of the inoculation of rabbits' blood into guinea-pigs, interesting toxic (anaphylactic) phenomena were frequently observed—abdominal distention, coma, spasm of the hind legs, scratching of the face and other symptoms of this complex which are well known. These symptoms have been described by others,² following intraperitoneal inoculation of rabbit serum, as well as local necrosis,³ which, however, we did not encounter in the course of our many subcutaneous injections. It seemed to us as if the toxic symptoms were more frequent and more marked in instances in which blood was injected from rabbits suffering from bovine tuberculosis. Accordingly we undertook an extended series of tests, summarized in Table 6, to gain a clearer understanding of this reaction. It became evident that our impression was correct, that pigs injected with normal blood or the blood of rabbits inoculated with a culture of the human tubercle bacillus reacted less regularly and with less intensity than did those inoculated with an equal amount of the blood of rabbits suffering from tuberculosis of the bovine type. Guinea-pigs inoculated with the blood from the bovine rabbits frequently died with symptoms simulating anaphylactic shock. Serum stored in the refrigerator for some days retained this toxic property. The toxicity cannot be explained by the fact that in the one case we were testing the blood of a markedly diseased animal, and in the other that of an animal which was almost normal, for the blood of rabbits suffering from rabies did not possess similar toxic properties. In this connection it should be mentioned that Friedberger and Schuetze⁴ were able to extract anaphylatoxin in the test tube from tubercle bacilli, by adding normal guinea-pig serum and complement. The amount of toxin obtained varied according to the proportion of antigen, serum, and complement used, and the period of extraction. Our results con-

1. Koehlisch: *Ztschr. f. Hyg.*, 1911, lxxviii, 193.

2. Thomson, O.: *Ztschr. f. Immunitätsf.*, 1909, i, 741.

3. Pfeiffer: *Ztschr. f. Hyg.*, 1897, xxvi, 384.

4. Friedberger, E. and Schuetze, A.: *Ztschr. f. Immunitätsf.*, 1911, ix, 431.

stitute a confirmation *in vivo* of these test-tube experiments; their lack of absolute regularity must be attributed to the variability of the diverse controlling factors.

CONCLUSIONS

For an experiment such as we set ourselves, namely, to determine the relation of virulence of bacteria to their persistence within the blood-stream, the tubercle bacillus would seem to be especially suitable. Apart from the fact that it multiplies so slowly, that this factor is negligible in a test of short duration, it occurs in two types, one feebly virulent to rabbits the other highly virulent. Morphologically these bacteria are almost identical; their preeminent difference is one of virulence. Accordingly definite quantities of these closely related microorganisms were inoculated into rabbits, and bleedings were carried out from one-half to four hours later to discover whether bacilli were still circulating in the blood. In a series of tests of this nature it was found that the feebly virulent human type of bacillus was present in only 9 per cent. of the tests, whereas the virulent bovine bacillus persisted in the blood-stream in 59 per cent. of the cases. These results seem to warrant the conclusion that virulence plays an important rôle in bacteremia, and that the bacteria may not be filtered from the blood by the tissues like inert foreign bodies. The fact that an avirulent bovine strain did not persist in the circulation strengthened us in this conclusion.

It is remarkable for how long a period after inoculation bacteria may still be found in the general circulation. In one instance in which but 1 mg. of bovine culture was inoculated, these bacilli were constantly found in the blood at various intervals during the subsequent twenty-seven hours. A period intervenes some days after inoculation during which even the virulent organisms are not found in the blood. However, this constitutes merely an intermediate or latent phase, and is followed by another phase cycle, in which, owing to the tuberculous condition of the animal, there is a reinvasion of the general circulation. For example, in tests performed a week or two subsequent to inoculation no bacilli were found, whereas in tests repeated a month later, when systemic tuberculosis had developed, bacilli were frequently demonstrated. These generalizations are subject to exception; in the case of one animal, although tubercle bacilli were obtained from the blood, autopsy some weeks later failed to reveal any tuberculous lesion.

In the course of a large series of injections, the interesting and suggestive phenomenon was noted, that the blood of the highly tuberculous rabbit is more toxic for the guinea-pig than that of the normal rabbit.

THE RELATION OF URICOLYSIS TO SUBOXIDATION *

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The later investigations in purin metabolism have disclosed the fact that there are clearly defined differences between man and other animals with respect to the ultimate products of the disintegration of the purin nucleus. In all mammals, man excepted, uric acid undergoes oxidation prior to excretion, so that in the dog, for example, a large part of the preformed uric acid is found in the urine as allantoin. Likewise in those mammals that excrete allantoin in appreciable amounts, it has been possible to demonstrate in the organs, usually liver and kidney, an enzyme that is capable of destroying uric acid—uricase. Up to the present all efforts directed toward disclosing uricase in man have met uniformly with negative results, and Wiechowsky has shown that if uric acid is destroyed at all in the human body it can hardly be by oxidation, since the diurnal allantoin excretion averages only a milligram. There is no direct evidence with respect to man which conclusively demonstrates that uric acid formed in the body undergoes chemical change before excretion, and it has been suggested that no such destruction occurs. Evidence pointing toward uricolysis is indirect inasmuch as the theoretical amount of uric acid resulting from ingested nucleins is not recoverable in the urine. The chemical possibilities other than simple oxidation which might explain uric acid destruction in the human organism do not concern us at present, further than to note regarding them that none is demonstrated.

It is an old idea that abnormalities in purin physiology are explicable as a simple retardation of normal processes—"delayed metabolism"; later this conception became more concrete in fixing the blame on the oxidative functions in general (Bouchard¹). When it became evident that the respiratory exchange might be quite normal even with perverted purin katabolism (Magnus-Levy²), the hypothesis of diminished oxidation was narrowed down to specific cellular processes (Ebstein³), which it was postulated might conceivably suffer without appreciably affecting

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1. Bouchard: *Les maladies par valentissement de la nutrition*, 1890.

2. Magnus-Levy: *Ueber Gicht*. *Ztschr. f. klin. Med.*, 1899, xxxvi, 353.

3. Ebstein: *Vererbbare zelluläre Stoffwechselkrankheiten*, 1902.

the sum of the oxygen exchange. To those who leaned strongly to the idea that oxidation, in some way or other, must be accounted the important factor in perverted purin metabolism the observation of Münzer was grist to the mill. He noted an increased uric acid excretion following poisoning with carbon monoxid and more recently Paton has recorded astonishingly high figures for uric acid excretion in coal-gas poisoning.

Because of the theoretical importance of these observations the subject of diminished oxidation in its relation to uric acid excretion was investigated. The question is reduced to its simplest terms in the dog, where allantoin, a direct oxidation product of uric acid, is excreted in the urine in considerable amounts. Naturally if this allantoin is a derivative of uric acid and is dependent on some oxidizing enzyme for its presence, then an interference with the oxidizing process might increase the uric acid output.

Interference with the absorption of oxygen by the body can arise in two ways—(1) By effecting chemical change in the hemoglobin that prevents it from combining with oxygen and fulfilling its carrying function. Carbon monoxid poisoning induces this result.⁴ (2) By decreasing the oxidative power of the cells themselves so that while the oxygen supply may be sufficient the tissues are not capable of utilizing this oxygen. Cyanid is the best example of poisons that reduce cellular oxidation.⁵

AUTHORS' EXPERIMENTS

Our experiments were conducted as follows: The dogs were fed on a uniform weighed diet of hashed meat, cracker meal, lard and water. After a suitable fore-period the animals were given varying amounts of potassium cyanid hypodermatically. Three doses were given daily—at 10 a. m. and at 4 and 10 p. m. The doses varied according to the resistance of the animal and were between 10 and 14 mg. per kilo body weight. The cyanid in all cases was forced to what seemed the maximum tolerance. A short period of vomiting was followed in some cases by convulsions, more commonly by a stuporous state. Feedings were so arranged that no loss of food resulted from the vomiting following the injection of the cyanid.

The results of the experiments with dogs are shown in Table 1.

It is possible that uric acid may undergo some destructive change in the human body other than a simple oxidation to allantoin. The observations of Paton⁷ and Münzer⁸ suggest that oxidation is an important step

4. Haldane: *Jour. Physiol.*, 1896, xviii, 201 and 430.

5. Marthen: *Arch. f. path. Anat. u. Physiol.*, 1894, cxxxvi, 535.

6. Geppert: *Ueber des Wesen der Blausäurevergiftung*, Berlin, 1889.

7. Paton and Eason: *Jour. Physiol.*, 1901, xxvi, 166.

8. Münzer and Palma: *Zeitschr. f. Heilkunde*, 1896, xv, 185.

in such a transformation. Cases of illuminating gas poisoning that were brought into the New York Hospital were utilized to test this hypothesis. A careful selection was made among the cases presented for study since we had no means of knowing at once for what periods the individual had been exposed to gas. When the "gas case" was brought into the

TABLE 1.—EFFECT OF CYANIDE ON DOGS
URINARY NITROGEN
DOG I

Date 1911	Total Nitrogen, Grams	Uric Acid Nitrogen, Grams	Purin Base Nitrogen, Grams	
March 25, 26.....	5.01	.0168	.0196	
March 27, 28.....	5.17	.0182	.0210	
March 29, 30.....	5.13	.0187	.0210	
March 31 and April 1.	4.65	.0165	.0154	KCN—25 mg. T. I. D.

DOG II

May 17, 18.....	6.41	.0185	.0174	
May 19, 20.....	6.45	.0193	.0178	
May 21, 22.....	6.04	.0182	.0169	KCN—35 mg. T. I. D.
May 23, 24.....	6.29	.0203	.0158	KCN—40 mg. T. I. D.

TABLE 2.—STUDIES OF URINE IN CASES OF GAS POISONING
URINARY NITROGEN

Case	Volume Urine, c.c.	Total Nitrogen, Grams	Ammonia Nitrogen, Grams	Uric acid, Grams
I, 2d. 24 h.....	770	15.22	.98	
3d. 24 h.....	610	14.56	1.13	.89
II	1710	26.18	1.05	.42
III	730	15.67	.56	1.46
				.86

URINARY SULPHUR

Case	Total Sulphur SO ₄ Grams	Total Sulphates SO ₄ Grams	Neutral Sulphur SO ₄ Grams	Neutral Sulphur Per cent. of Total S.
I, 2d. 24 h.....	2.70	2.20	.50	18
II	5.62	5.15	.47	8
III	2.69	2.57	.12	4

reception ward from the ambulance the patient was at once catheterized and the urine used for routine tests. After this the man was catheterized every six hours and the urine saved. If he remained unconscious for twenty-four hours the total urine for that period was used for study. If consciousness returned before the full day elapsed the collection was discontinued and study of the case abandoned. In this way only such

cases were utilized as had been exposed to gas for some time. Certain unavoidable sources of possible error exist in the employment of these cases. We have no knowledge of the food taken before narcosis. Also all patients were subjected to phlebotomy as a therapeutic measure, but since this is a common factor it is not a serious obstacle in the investigation.

The results of the analyses of the urines are recorded in Table 2. In the first place it is to be noted that the uric acid excretion while high, is not without the bounds of normal for the conditions of this experiment. Carbon monoxid poisoning causes a marked stimulation of katabolic processes; the high nitrogen excretion represents one phase and the uric acid another. No such amounts of uric acid were excreted as were recorded by Paton and one is not justified in ascribing the rather high excretion found to diminished oxidation primarily, since it may be wholly accounted for by other factors. A most surprising fact is that only one of these cases (Case 1) presents tangible evidence of cellular suboxidation. In this case the amount of unoxidized (neutral) sulphur is such a large proportion of the total that diminished oxidation is probably the explanation. This case was apparently profoundly poisoned, judging from the period of coma. In the other cases no such condition was found, yet the uric acid excretion was even greater in some of them.

It is shown by results of analyses here presented that retardations of the oxidizing processes, either by deprivation of oxygen or by interference with cellular functions, were not followed by increased uric acid excretion. It appears improbable, therefore, that uric acid destruction in the body is a simple oxidizing process.

THE SCAPHOID SCAPULA: A NORMAL VARIATION IN MAN *

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Dr. Graves¹ has recently called attention to a type of scapula which he designates as "scaphoid." The character of the vertebral border determines whether a scapula is scaphoid or not. Our best known anatomical text-books² describe the vertebral border as "arched," "of curved or somewhat irregular outline" and "nearly vertical from the lower angle to the triangular smooth place on the dorsum opposite the spine." Morris³ does not mention the curve of the vertebral border, but agrees with the other authors in figuring the bone with a vertebral border gently curved toward the spinal column. Thomas Dwight,⁴ in speaking of the variations of the vertebral border, states:

The most common form of the scapula presents a line slightly curved at the lower part and then straight as far as the root of the spine, from which point it inclines slightly forward till it ends at the upper angle. The forward inclination of the upper part, though varying in degree, is, so far as I know, constant, but the rest of the line varies much. Sometimes it is almost straight, sometimes the whole border of the bone is convex, sometimes the border below the spine is concave.

These scapulae with vertebral borders concave below the spine Graves designates as "scaphoid." He finds them differing from the convex type of scapula, first, in having a scapular index of 2.3, less than that of the average type; second, in having vertebral borders more nearly parallel to the long scapular axis; third, in having a spine, as a rule, more nearly at right angles to the long scapular axis; fourth, in having poorly marked anterior and posterior lips, and intermediate surface of the vertebral border, and fifth, in possessing tuberosities varying in size and number, frequently found along the vertebral border, which he calls "border buds."

As normal variations they are of passing interest, but considered as "A Frequent Anomaly in Development of Hereditary, Clinical and Anatomical Significance," they at once demand attention.

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¹From the Hearst Anatomical Laboratory of the University of California.

1. Graves: The Scaphoid Scapula. A Frequent Anomaly in Development of Hereditary, Clinical and Anatomical Significance. Med. Rec., New York, May 21, 1910.

2. Gray: Anatomy; Cunningham: Text-Book of Anatomy; Piersol: Human Anatomy.

3. Morris: Human Anatomy.

4. Dwight: The Range of Variation of the Human Shoulder Blade. Am. Nat., 1887.

Among 198 dry bones Dr. Graves found
 121 or 61 per cent. convex or "normal,"
 51 or 26 per cent. straight,
 26 or 13 per cent. concave or scaphoid.

Among 72 dry bones examined here
 34 or 47 per cent. were convex,
 19 or 26 per cent. straight,
 19 or 26 per cent. concave or scaphoid.

From this we see that the scaphoid scapula is of frequent occurrence.

The claim made for its hereditary and clinical significance may be judged from the title to Dr. Graves'⁵ article, "The Scaphoid Scapula Syndrome: Its Connection with Syphilis in the Ascendants."

TABLE 1.—RESULTS OF MEASUREMENTS OF SCAPULAE OF MEN

	—Normal—			—Scaphoid—			
	No.	No.	Result	No.	No.	Result	
	Obs.	Cases	Obs.	Cases	
Wing-like scapulae, both....	134	99	74.0	119	80	67.0	Per cent.
Prom. acrom.-clav. artic....	134	88	65.0	119	72	60.0	Per cent.
Clavicles — or \wedge *.....	134	54	40.0	119	58	48.0	Per cent.
Abnormal chests	129	41	31.8	109	50	46.0	Per cent.
Spinal curves	128	45	34.0	109	38	35.0	Per cent.
Palpable glands	129	15	11.0	109	9	8.0	Per cent.
Adenoids operated	129	8	6.2	109	3	2.7	Per cent.
Tonsils operated	129	14	10.9	109	14	12.0	Per cent.
Tonsils enlarged	129	19	14.8	109	19	17.0	Per cent.
Abnormal hearts	129	6	4.7	108	3	2.7	Per cent.
Abnormal lungs	129	0	0.0	108	1	.9	Per cent.
Blood-pressure (standing)...	120	..	114.6	108	..	120.5	mm. Hg.
Blood-pressure (sitting)	118	..	120.3	108	..	121.6	mm. Hg.
Average age	129	..	20.3	108	..	19.8	Years
Average weight	98	..	62.3	88	..	64.1	kilos
Average height	98	..	1715.0	91	..	1747.3	Centims
Average lung capacity.....	95	..	4.15	91	..	4.23	Liters
Lung cap'y less than 2.5 L.	Per cent.
General development, excellent	129	21	16.0	108	19	17.6	Per cent.
General development, good...	Per cent.
General development, average.	129	88	68.0	108	73	67.6	Per cent.
General development, fair....	Per cent.
General development poor....	129	20	16.0	108	16	14.8	Per cent.
Parents foreign	258	76	29.0	216	65	30.0	Per cent.
Parents dead	258	32	12.4	216	20	9.0	Per cent.
No. children per family.....	129	511	3.9	108	414	3.8	Per fam.
Death-rate	129	36	.27	108	36	.22	Per fam.

*Horizontal or elevated at sternum.

Anatomically, individuals with scaphoid scapulae are said to differ from average individuals in having longer necks, clavicles more nearly in a horizontal line, more prominent acromio-clavicular articulations and more prominent "wing-like" inferior angles to their shoulder blades.

If scaphoid scapulae are due in any way to syphilis in the ascendants, we would expect to find in individuals having scapulae of this type other evidences of "blight," among which Graves mentions, deviating characteristics of the whole individual, the presence of arteriosclerosis at unusually early periods of life, disharmony in physical and mental devel-

5. Graves: The Scaphoid Scapula Syndrome: Its Connection with Syphilis in the Ascendants. Interstate Med. Jour., 1911, xviii, No. 1.

opment, abnormal degree of lymph-node palpability, relative frequency of adenoids, frequent catarrhal affections developing early in infancy and persisting for years, and nocturnal incontinence.

In order to get an idea of the occurrence of the scaphoid scapula and to work out its syndrome from a large number of seemingly average individuals, measurements of the shoulder blades of incoming students of the University of California were made in August, 1912. The relative heights of the two shoulders, the length of the neck, the angle made by the clavicles, the prominence of the acromio-clavicular articulation, and the prominence of the inferior angle of the scapula were noted and recorded.

On entrance to the university all students are given a rigid medical and physical examination. As soon as they were dismissed by the medical examiner they presented themselves for the scapular measurements. The subject stood erect and quiet for a few moments. The vertebral borders of the scapulae were palpated with the index finger and carefully outlined with a blue wax pencil. The prominent bony part of the dorso-lateral extremity of the acromion process was marked and by pressing the full length of the index finger against the caudal border of the crest of the spine the direction of the spine was determined and marked in blue pencil.

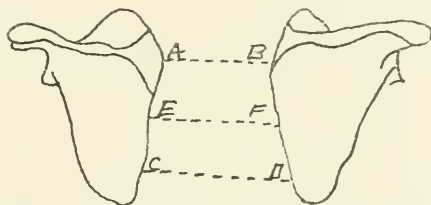


Fig. 1.—Showing method of determination of variety of scapula.

To be sure that the scapulae had not changed in position and that the lines and points were correctly marked, all of the lines of both scapulae were palpated a second time.

The distance between the vertebral borders of the scapulae at the bases of the spines was measured and recorded as distance AB (Fig. 1). About $11\frac{1}{2}$ inches from the inferior angle, a second measurement of distance between the vertebral borders was taken and recorded as CD . Half-way between AB and CD , a third measurement, EF , was made.

If the average length of AB and CD ($\frac{AB + CD}{2}$), is greater than EF , the scapulae are convex toward each other. If the average of AB and CD is equal to EF , the vertebral borders are straight, and if the average is less than EF , the scapulae are concave toward one another or scaphoid.

In most cases little difficulty was encountered in palpating the points and lines desired, but among the women one swimmer, one violinist, a few obese individuals and several others, offering difficulties of measurement, were allowed to pass unrecorded.

In order to select groups having greatest concavity of scapular border, only those having *EF* greater than the average of *AB* and *CD* by more than 1 cm. were considered typically scaphoid, and all having vertebral borders in any degree convex toward each other were considered "normal."

In all, 1,067 individuals were measured with the following results:

	— Men —		— Women —		— Total —	
	No.	Per cent.	No.	Per cent.	No.	Per cent.
"Normal"	134	21	150	36	286	27.0
Straight	120	19	47	11	167	15.8
Scaphoid by less than .5 cm....	104	16	102	24	206	19.5
Scaphoid by from .5 to 1 cm....	164	26	76	18	240	22.6
Scaphoid by over 1 cm.....	117	18	43	10	160	15.1

In order to determine if the scaphoid individuals, as a class, show evidences of "blight," the 134 "normal" men have been contrasted with the 117 decidedly scaphoid men, and the 150 "normal" women with the 43 decidedly scaphoid women.

The following tables give the results of the measurements together with other data bearing on the problem. Weights, heights and lung capacities were obtained from the gymnasium records, and the other items from the records of the medical examiners.

Chests were recorded as normal, flat, funnel or pigeon-shaped. All of those not recorded as normal were here classed as abnormal. Spinal curves were recorded as normal, lordosis, scoliosis and kyphosis. All other than normal were grouped as abnormal even though the abnormality was marked (slight). Palpable inguinal, axillary and cervical glands were recorded. Tonsil and adenoid observations were made by a specialist. Blood-pressure was measured by a Mercer apparatus accurate to 5.00 millimeters. Heart action was recorded as regular, irregular or intermittent. Where functional disorders were present note was made of the fact. All not marked regular were here classed as abnormal. Lungs were marked negative or special, and note was made of the abnormal respiratory sounds. Under general development such factors as stature, nutrition and general muscular tone, were considered.

The comparative figures do not show that the scaphoid scapula is especially associated with blight or disharmonies. Among both the men and women the average age for entering college is lower for scaphoid than for "normal" individuals which argues well for mental development. Average weights and heights of the two classes are hardly sufficiently different to be worthy of note. The "normal" women average a little heavier and the scaphoid a little taller, while the scaphoid men are both heavier and taller. Among the women there is slightly less lymph-node tonsil and adenoid enlargement in those of the scaphoid group, whereas among the men the scaphoid group show less lymph-node and adenoid difficulty, but a higher percentage of tonsil operation and tonsil enlargement.

The blood-pressure comparisons are of especial importance on account of the fact that the arterial changes shown by those having scaphoid scapulae lead Graves to suspect syphilis as one cause of the imperfect development of the scapula.

Among the women the average blood-pressures of the normal and scaphoid groups are identical within the limit of error of the apparatus. Among the men those with scaphoid scapulae show a slightly higher blood-pressure, both when standing and when reclining.

TABLE 2.—RESULTS OF MEASUREMENTS OF SCAPULAE, ETC., OF WOMEN

	—Normal—			—Scaphoid—			
	No. Obs.	No. Cases	Result	No. Obs.	No. Cases	Result	
Wing-like scapulae, both....	136	41	30.0	38	14	37.0	Per cent.
Wing-like scapula, one.....	136	27	19.8	38	8	21.0	Per cent.
Prom. acrom.-clav. artic.....	136	72	52.9	38	17	44.7	Per cent.
Clavicles — or \diagup *	136	45	33.0	38	13	34.2	Per cent.
Abnormal chests	136	42	30.8	38	14	36.8	Per cent.
Spinal curves	136	18	13.2	38	4	10.5	Per cent.
Palpable glands	136	24	17.6	38	6	15.8	Per cent.
Adenoids operated	136	11	8.0	38	2	5.2	Per cent.
Tonsils operated	136	10	7.3	38	1	2.6	Per cent.
Tonsils enlarged	136	10	7.3	38	2	5.2	Per cent.
Abnormal hearts	136	12	8.8	38	4	10.5	Per cent.
Abnormal lungs	136	6	4.4	38	2	5.2	Per cent.
Blood-pressure (standing) ..	136	..	120.6	38	..	120.5	mm. Hg.
Blood-pressure (sitting)	136	..	116.0	37	..	116.8	mm. Hg.
Average age	118	..	21.8	32	..	20.2	Years.
Average weight	83	..	53.6	15	..	52.7	Kilos
Average height	86	..	1617.0	15	..	1620.0	Centim.
Average lung capacity	85	..	2.53	15	..	2.34	Liters
Lung cap'ty less than 2.5 L. .	85	30	35.0	15	5	33.0	Per cent.
General development, excellent	136	9	6.6	38	0	0.0	Per cent.
General development, good...	136	34	25.0	38	6	15.8	Per cent.
General development, average	136	71	52.2	38	16	42.1	Per cent.
General development, fair...	136	19	14.0	38	15	39.5	Per cent.
General development, poor...	136	5	3.7	38	0	0.0	Per cent.
Parents, foreign	272	67	24.6	76	12	15.7	Per cent.
Parents, dead	272	32	11.7	76	10	13.2	Per cent.
No. children per family.....	136	557	4.10	36	141	3.91	Per fam.
Death rate	136	56	.41	36	24	.66	Per fam.

*Horizontal or elevated at sternum.

The variations throughout the tables are quite such as one might expect to find in comparing two groups of equal numbers selected at random.

So far we are led to conclude that among average individuals between the ages of 16 and 25 the scaphoid type of scapula is of frequent occurrence, but of no clinical significance.

In order to contrast a group of deviates with the student class already studied, 442 inmates of the State Home for the Feeble-Minded at Sonoma, Cal., were examined.

It was quite impossible to get them in good attitudes and keep them quiet so as to outline the vertebral borders of the scapulae and measure them, so palpation had to be depended on.

With the entire length of the index finger of one hand pressed against the caudal edge of the spine of the scapula and directed toward the vertebral border the base of the spine was located. The index finger of the other hand was placed on the vertebral border at this place and the other three fingers spread out along the caudal part of the vertebral border. By their position and by moving them up and down along the vertebral border its character could quite easily be determined, unless it was on the border line between convex and straight or concave and straight. In many

TABLE 3.—TOTALS OF TABLES 1 AND 2

	—Normal—			—Scaphoid—			
	No. Obs.	No. Cases	Result	No. Obs.	No. Cases	Result	
Wing-like Scapulae	270	140	51.8	157	94	60.0	Per cent.
Prom. acrom.-clav. artic.....	270	160	59.0	157	89	56.6	Per cent.
Clavicles — or \wedge *	270	99	36.6	157	71	45.2	Per cent.
Abnormal chests	265	83	31.3	147	64	43.5	Per cent.
Spinal curves	264	63	24.0	147	42	28.6	Per cent.
Palpable glands	265	39	14.7	147	15	10.2	Per cent.
Adenoids operated.....	265	19	7.1	147	5	3.4	Per cent.
Tonsils operated	265	24	9.0	147	15	10.2	Per cent.
Tonsils enlarged	265	29	10.9	147	21	14.3	Per cent.
Abnormal hearts	265	18	6.8	146	7	4.8	Per cent.
Abnormal lungs	265	6	2.2	146	3	2.0	Per cent.
Blood-pressure (standing) ..	256	..	117.6	146	..	120.5	mm. Hg.
Blood-pressure (sitting)	254	..	118.15	145	..	119.2	mm. Hg.
Average age	247	..	21.05	140	..	20.0	Years
Average weight	181	..	58.45	103	..	58.4	Kilos.
Average height	184	..	1666.0	106	..	1683.6	Centims.
Average lung capacity	180	..	3.34	106	..	3.28	Liters
Lung cap'ty less than 2.5 L..	85	30	35.0	15	5	33.0	Per cent.
General development, excellent	265	30	11.3	146	19	13.0	Per cent.
General development, good....	136	34	24.0	38	6	15.8	Per cent.
General development, average	265	159	60.0	146	89	60.6	Per cent.
General development, fair ...	136	19	14.0	38	15	39.0	Per cent.
General development, poor....	265	25	9.4	146	16	10.9	Per cent.
Parents foreign	530	143	27.0	292	77	26.0	Per cent.
Parents dead	530	64	12.0	292	30	10.2	Per cent.
No. children per family.....	265	1068	4.03	144	555	3.85	Per fam.
Death-rate	265	92	.34	144	60	.41	Per fam.

*Horizontal or elevated at sternum.

such cases it was impossible to judge positively of the nature of the border, and it was recorded as questionable or straight. For this reason the figures indicate a lower number of convex and scaphoid scapulae and a higher number of the straight scapulae than if they had been measured.

On account of the impossibility of making measurements on the deviates, exact comparisons cannot be made between them and the student class.

However, the comparisons are suggestive:

	Student Class, Per cent.	Deviate Class, Per cent.
Convex vertebral borders	27	22
Straight vertebral borders.....	15 (straight and questionable)	52
Concave vertebral borders	57	26

Had the student class been palpated instead of measured, many of those here classed as normal and apparently scaphoid, would have been put with the questionable or straight.

The Wassermann test for syphilis has been made by Dr. Linforth on practically all of the women of the Sonoma State Home. Of the 304 whose scapulae were measured, eight gave a positive test. Of these none was under 16 years of age, so that in no case could we safely assume that the disease was congenital. However, among the eight, three had convex scapulae, three straight or questionable scapulae and two scaphoid scapulae.

Since among over 1,000 college students those with scaphoid scapulae show no "blight," and since "normal" scapulae are almost as frequent among deviates as among students, and scaphoid scapulae as frequent among students as among the feeble-minded, there seems to be little cause to consider it an anomaly or to hunt for an explanation for the condition in the history of the individual or his ascendants, and we must, with Thomas Dwight, consider as a normal variation scapulae in which "the border below the spine is concave."

TABLE 4.—TURNER'S FIGURES ON SCAPULAR AND INFRASPINOUS INDICES OF VARIOUS RACES

Race	No. of Scapulae	Scapular Index	Infraspinous Index
Lapps	8	62.0	85.9
Esquimaux	8	61.0	81.3
Tasmanians	6	60.3	81.4
Australians	28	64.9	88.5
Bushmen	10	66.2	89.7
Polynesians	32	66.6	89.4
Peruvians	46	66.5	89.6
Fuegians	9	65.0
Europeans	462	65.3	87.8
Negroes	100	69.7	98.5
Andamanese	27	70.2	97.3
Melanesians	26	69.8	93.8
Malayians	10	68.9	93.8

Much attention was directed to the scapula by the paper read by Broca before *La Société d'Anthropologie* in 1878, in which he defined scapulae and infraspinous indices, and proposed them as methods of determination of race. He found Negroes, Andamanese and Australians to have high indices, which means broad scapulae, and speaks of them as "consequently of a lower type," having already pointed out the fact that in all orders of animals, except bats, the scapular index is greater than in man.

During the following year many measurements of scapulae were undertaken. Thomas Dwight, of Harvard, collected what data he could from others, and adding to them his own findings, largely obtained from bones of American Indians, published an article in the July *American Naturalist*, in 1887, on "Variations of the Human Scapula," in which he concluded that the Kentucky Mound Builders had decidedly higher indices, or, in other words, broader scapulae, than the Caucasians.

Dorsey, on the contrary, found the West Coast Indians to have a mean scapular and infraspinous index lower than any yet recorded for any race except Esquimaux, Hottentots and Tasmanians.

Sir William Turner, in his "Report on the Bones of the Human Skeleton," gives the figures shown in Table 4.

In conclusion to his comparison of the scapulae he says:

Should there be anything in the habits of one race of men which might require a particular group of scapular muscles to be used and developed to an extent far greater than in another race, then it is not unlikely that the area of attachment of these muscles in that race would be widened and lengthened to an extent greater than in the case of those races in which the same group is not similarly exercised, and the proportion of those parts of the scapula to the rest of the bone would in so far be modified. The arboreal habits of the ape require that it should use its upper limbs for purposes of climbing and for swinging itself from one branch of a tree to another, so that the muscles engaged in the elevation of the upper limb require to be powerful, which would account for the greater development of the supraspinatus muscles and fossa, and would probably lead also to the greater obliquity of the scapular spine than in the case of man. In a similar manner one would expect to find in those races of men, as the Australians, who climb trees in quest of food, or those natives in the interior of New Guinea, whose houses are built in the upper branches of lofty trees, a commensurate development of the elevatory muscles of the upper limb and of their respective areas of attachment. But in connection with this development, the additional area might be obtained, either by an addition to the length or breadth of the surface, or perhaps both to the length and breadth.

Considering the subject from an evolutionary point of view and accepting the underlying idea of Sir William Turner's quotation, we may consider that as a primitive race we inherit broad scapulae with convex vertebral borders and those races making much use of their shoulder muscles have best preserved such scapulae; that among civilized races where the arms are comparatively little used decrease in size has followed decrease in use. The decrease may be either in length or breadth or both and may account for the scaphoid scapula.

Since evidence for considering the scaphoid scapula as an anomaly of development is lacking, and since it is possible that man's upright position might lead to such a variation from the animal type, it seems logical from the biological standpoint, as well as from the clinical, to consider the scaphoid scapula as a normal variation.

In addition to the references numbered in the text the following are given:

Mivart: Appendicular Skeleton of the Primates. *Phil. Trans.*, 1867, clvii, 304.

Graves: The Clinical Recognition of the Scaphoid Type of Scapula and Some of Its Correlations. *Jour. Am. Med. Assn.*, 1910, iv, 12.

Kollert: Ueber die Skaphoide Form des Schulterblattes. *Wien. klin. Wchnschr.*, 1911, No. 37.

Kellner: Ueber Scapular Scaphoideae. *Deutsch. med. Wchnschr.*, 1911, p. 91.

Turner: *Challenger Reports*, Vol. xvi.

Dorsey: Observations on the Scapulae of the Northwest Coast Indians. *Am. Nat.*, 1897, p. 736.

Kingsley: Foramina of Scapulae. *Science*, N. S., 1900, ii, 167.

Schuck: Das Schulterblatt des Menschen und der Anthropoiden. *Mitt. d. anthropol. Gesellsch.*, 1910, Wien, xl, 231.

ERYTHREMIA, OR POLYCYTHEMIA WITH CHRONIC CYANOSIS AND SPLENOMEGALY

REPORT OF TWO CASES WITH A SUMMARY OF 179 CASES
REPORTED TO DATE *

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Renewed interest has recently been shown in that primary form of polycythemia with chronic cyanosis and splenomegaly which was first brought to the attention of the profession in 1892 by H. Vaquez,¹ and which has been well termed "erythremia" in contra-distinction to "erythrocytosis" or secondary polycythemia.

Erythremia was long considered a rare condition and as late as 1907 Mackey,² in a most excellent thesis, was able to cite but about forty cases. During the past few years, however, the increasing number of patients reported from various sources indicates that the malady is not by any means as uncommon as was at first supposed. Indeed, Staehelin,³ in 1911, reported eleven cases of polycythemia which came under his observation in a single year, of which at least six appear to have been of the Vaquez type.

As the result of a recent careful search through medical literature, I have succeeded in collecting reports on 179 cases of so-called polycythemia, of which 149 cases appear to be unquestionable instances of erythremia, the other thirty cases being open to doubt as to their true classification.

The two cases which have come under my observation and which aroused my interest in the condition are as follows:

CASE REPORTS

CASE 1.—B. W., male, married, white, aged 52, a native of Russia, grocer, was admitted to the service of Dr. H. A. Hare in the Jefferson Medical College Hospital, May 19, 1911. Family history is unimportant; no history of malignant or tuberculous disease.

*Manuscript submitted for publication July 15, 1912.

*Ten additional cases have been collected since this paper was prepared for publication and too late to permit of their inclusion under the proper classification in the summary at the end of this article. These ten cases have been shown separately at the end of the summary, thus making a total of 189 cases in all.

1. Vaquez, H.: *Compt. rend. Soc. de biol.*, 1892, series 9, p. 384; also *Bull. méd.*, Paris, 1892, vi, 849.

2. Mackey: *Birmingham Med. Rev.*, 1907, N. S., lxii, 113 and 177.

3. Staehelin: *Berl. klin. Wehnschr.*, 1911, xlviii, 101.

Patient had measles in childhood. At the age of 20 he had an attack of pleurisy, was seriously ill and had a cough for some time subsequent but afterward became perfectly well.

On Feb. 5, 1906, he was operated on at the German Hospital by Dr. John B. Deaver for a prostatic abscess, which was opened through the perineum and drained with an uneventful recovery. Subsequent to this operation he noticed that his color was changing and he became blue. Is said (by himself) to have had a puncture in the right kidney region and that pus was found, this operation being within a comparatively short time after the other. The physician who did this puncture has since died.

At about this time he went to the Pennsylvania Hospital on account of failing vision, dizziness, etc. His symptoms then were the same as at present; namely, headache, vertigo, hazy vision and a feeling as though his head was stuffed with blood.

From that time his general health was good with the exception of attacks of "asthma," cough and shortness of breath, up to May, 1910, when he began to have attacks of headache, confined to the right side of his head, and accompanied by dizziness and shortness of breath. Following these attacks his hands, face, lips and nose became dusky, the duskiness lasting from two to twenty-four hours.

Beginning in the Autumn of 1910 he had frequent attacks of indigestion which seemed to precede the attacks of cyanosis and headache.

Since January, 1911, he has had considerable difficulty with his eyes, stating that he has scarcely been able to read a newspaper and that he has had a continual haze over his eyes and that stooping or suddenly turning his head brought on dizziness and cyanosis. He also complained of a lump in the throat on swallowing.

Examination.—Patient is a well nourished and well developed adult. Skin is dry and warm. His face, and especially his nose, lips, cheeks and ears are of a bluish-red color. The hands, wrists and arms to elbows are bluish-red. Dorsum of feet present nothing abnormal but the soles both are bluish-red and somewhat edematous. The tongue is red and coated with grayish fur. The pharynx is purplish red.

Fingers are clubbed with slightly curved nails.

The examination of the abdomen proved negative, the liver not being enlarged and the spleen showing no enlargement except on one occasion, during an exacerbation, when it was very slightly enlarged.

The chest is symmetrical; expansion equal and full; hyperresonant throughout; a few moist râles heard over both bases. Respiration 22.

Heart sounds rhythmical, distant at apex, maximum intensity in epigastrium where the sounds are clear. Pulse 92. Blood-pressure, systolic 120, diastolic 86.

None of the superficial lymph-nodes palpable.

Genitals negative. A scar observed two inches below last rib on right side.

Wassermann test proved negative.

X-ray examination reveals many enlarged mediastinal glands.

Eyes: Pupils dilated, equal and react normally. Double optic neuritis with four diopters of swelling in each eye and hemorrhages into the retina. Vision about one-half normal with glasses. Fields concentrically contracted about one-half. (See subsequent reports.)

Temperature 98.6.

Urine: Slightly turbid, amber, 1.019, acid; faint trace of albumin; no sugar, crystals, blood or casts; a few urates, epithelial cells and leukocytes. Urea 2 per cent. Practically the same on a number of subsequent examinations. Quantity during first week in hospital averaged 500 c.c. for twenty-four hours; next two weeks averaged 1,200 c.c., dropping to an average of 700 c.c. during rest of stay. During second short stay in hospital the average was 500 c.c.

Course.—Patient's temperature on admission was normal and during his stay ranged between 97 and 99 F. with one rise of short duration to 100.6 and one drop to 96.4.

From May 20, 1911, the day after admission, to June 14, 1911, date of discharge, his weight dropped from 129.5 to 120 pounds.

Pulse rather irregular, ranging between 80 and 100 with one rise to 110 and one drop to 74. His respiration was usually about 22 although occasionally as high as 30. Bowels moved once or twice daily with, occasionally, laxatives.

His cyanosis continued throughout his entire stay in the hospital. Until May 20 he was free from headaches and dizziness but on that date had several attacks of dizziness, lasting a few minutes each, and also a slight right-sided headache.

On May 21 he had two brief attacks of dizziness due to suddenly turning the head to the side and stooping. Also complained at this time of drawing sensation in calf of left leg.

Date	Erythro- cytes	Hgb.	C. I.	Leuko- cytes	Polymor- pho- nuclears, %	Lymphocytes per cent.	Hyaline per cent.	Remarks
1911								
5-12	7,810,000	135	.86	8,200	From finger
5-13	8,060,000	138	.86	8,800	54	20	15	From toe; also 9 per cent eosinophils and 2 per cent. degenerated eosinophils.
5-22	8,660,000	140	.81	8,000	57	27	8	Eosinophils 2 per cent. and neutrophilic myelocytes 6 per cent.
6- 9	7,900,000	129	.81	7,400	Before bleeding.
6- 9	6,530,000	127	.97	6,880	After bleeding.
6- 9	6,800,000	112	.82	7,200	80	15	6	No parasites. Morphologic characteristics correspond to normal red cells.
11- 9	6,470,000	125	.97	10,200	74	15	7	Eosinophils 2 per cent.; degenerated 2 per ct.
11-25	6,130,000	138	1.13	9,200	Before bleeding.
11-25	5,200,000	96	.92	7,500	After bleeding.

On May 23 again complained of being dizzy at irregular intervals.

On June 9, 16 ounces of blood removed from right median basilic vein. Was slightly improved on June 12 and was discharged on June 14.

Patient then felt very well until about the last of September, 1911, when old symptoms returned, and on November 8 he was readmitted, his condition in general being about the same as in June. The extremities at this time showed a slight pretibial edema. Eye examination revealed a swelling of two diopters in each eye. Vision 20/30 with glasses. Fields contracted about one-half as before. No hemorrhages. Every evidence of a subsiding inflammation with probably a secondary atrophy obscured by the inflammatory changes.

The patient received no medication at this time except laxatives and was up and around the ward the second day, apparently very comfortable and was discharged on November 13.

November 25, 1911, patient returned to ward for venesection to relieve symptoms of dizziness, his condition being about the same as before, 16 ounces of

blood being withdrawn from superficial vein of right elbow. No change was noted in his condition immediately following venesection but he felt better on the following day, his color being less dusky, and he was discharged with instructions to report to the out-patient department.

For some time thereafter he reported regularly at the out-patient department and was bled four times with temporary relief. An x-ray examination of the chest at this time showed the heart to be apparently of normal size, rather horizontally placed. There seemed to be multiple adhesions between the pericardium and the diaphragm; also marked thickening of the peribronchial glands.

No parasites or organisms of any kind were found in the blood at any time.

In January, 1912, the patient spent several weeks in the German Hospital, where, in addition to other treatment, he was subjected to treatment by the x-ray over the long bones. His condition at this time was about the same as before and he was not permanently benefited by treatment.

Recently he has been a patient at the Pennsylvania Hospital complaining of an exacerbation of symptoms. Dr. William T. Shoemaker, who examined the patient on both of the occasions when he was in the Pennsylvania Hospital, and who has kindly given permission to include the results of his observation of the eye-grounds, states: "Although, of course, interesting in many ways, special interest from an ophthalmic standpoint lies in the *violent* changes which are shown in the optic nerve, retina and blood vessels. These changes are those of *typical inflammatory choked disk*, identical, it would seem, with those frequently seen with intracranial disturbance."

The patient recently advised me that for some time he has been subject to periodic hemorrhages from the bowel, occurring on an average of once in six weeks and followed by some temporary relief.

Despite all treatment his general condition at present is about the same as when first seen.

CASE 2.—Male, aged 43, Russian Jew, vest-maker, was admitted to the service of Dr. H. A. Hare in the Jefferson Medical College Hospital April 22, 1912, complaining of severe headache, dyspnea, dizziness and nervousness. His bowels were constipated, appetite poor.

Family history unimportant; so far as he knows no member of his family has suffered in a similar way.

He came to the United States from Russia twenty years ago and since his arrival in this country has worked continuously as a vest-maker. For four years prior to leaving Russia he was a soldier.

For fifteen years he has been troubled with "asthma" and cough.

Suffered from hemorrhoids for fifteen years, undergoing an operation ten months ago for relief from same.

Has had more or less headache for six years.

Three months ago had a slight attack of hemoptysis.

Two weeks prior to admission he began to suffer from severe headache, dyspnea, dizziness and nervousness.

Two days prior to admission his wife called his attention to the change in his color. He is somewhat myopic.

Examination.—The patient is a well-nourished adult male.

His face is somewhat cyanotic, being markedly so when he lies down. The lips and ears are markedly dusky and the hands slightly so. The tongue is very red and the buccal mucosa and pharynx are bluish-red.

Spleen was not palpable.

Liver dulness was slightly increased.

Lungs: Prolongation of expiration and many rales throughout the chest. Resonance impaired anteriorly at the right apex and slightly impaired posteriorly at both bases. Respiration 32.

Heart: Faint systolic murmur at the mitral area. Muscle tone fairly good. Pulse somewhat rapid on admission (118), falling to 96 the following day.

Systolic blood-pressure 132.

Legs and feet swollen and edematous; pit on pressure.

Temperature 99.4 F. on admission; 98.4 the following day.

Eyes: React normally to light and accommodation. Pupils equal. There was a marked congestion of the conjunctiva and retina.

Urine: This showed a very faint trace of albumin; no casts.

Sputum: Negative as to tubercle bacillus.

Blood: The red cells were 8,430,000; hemoglobin 95 to 120; white cells 8,800 to 13,400. Polymorphonuclears 70 per cent.; small lymphocytes 16 per cent.; large lymphocytes 12 per cent.; eosinophils 2 per cent.; blood platelets four in one field.

X-Ray.—X-ray examination of the thorax revealed marked peribronchial thickening, particularly on the left side, and bronchiectasis.

Treatment.—Under treatment with morphin sulphate, atropin, epinephrin, oil of cloves, purgatives and, finally, elixir iron, quinin and strychnin, patient left hospital with general condition apparently considerably improved.

Six months later: Condition unchanged. Had several exacerbations and twice symptoms were sufficiently severe to require venesection, which gave prompt but only temporary relief.

SYNONYMS

Erythremia, or primary absolute polycythemia, is also known as Vaquez's disease, Osler's disease, polycythemia with chronic cyanosis, myelopathic polycythemia, splenomegalic polycythemia (Weber⁴), cryptogenic polycythemia (Cabot), and erythrocytosis megalosplenica (Senator⁵). The term erythremia, suggested by previous authors,⁶ seems especially appropriate, distinguishing the condition as it does from erythrocytosis,⁷ or polycythemia rubra of known origin, just as the terms leukemia and leukocytosis distinguish analagous condition in which the white cells are particularly affected.

It is probable that cases of erythremia were formerly reported under such headings as "plethora," "venous congestion with cyanosis," etc., and, as Herringham⁸ points out, Cuffer and Sollier's two cases⁹ of "congestive venous diathesis," reported in 1889, may have been examples of this disease.

HISTORY

In 1892, Prof. H. Vaquez,¹ of the Faculte Medicin, Paris, reported a case of peculiar cyanosis with persistent polycythemia, which he regarded as due to congenital heart disease. The liver and spleen were enlarged and the red cells and hemoglobin greatly increased. On the death of his patient in 1895, Vaquez discovered the absence of organic heart involvement.

4. Weber: Med. Chir. Tr., London, 1905, lxxxviii, 191.

5. Senator: Ztschr. f. klin. Med., 1906, lx, 357.

6. W. Turk, Hirschfeld and W. Osler.

7. This term was suggested by Hirschfeld.

8. Herringham: Brit. Med. Jour., May 9, 1908, i, 1096.

9. Cuffer and Sollier: Rev. de Med., Paris, 1889, xxii, 825.

In 1899, Rendu and Widal¹⁰ reported the case of a policeman with enlarged spleen, marked cyanosis and polycythemia. At autopsy the heart was found to be normal, but the spleen was tuberculous and contained large caseous areas. The bone marrow contained nucleated red cells pointing to over-activity. Rendu and Widal concluded that the disease was due to primary tuberculosis of the spleen, which conclusion has not, however, been sustained by subsequent investigation.

At about the same time two cases were reported by Cabot,¹¹ one by Cominotti¹² and one by McKeen.¹³

Erythremia was first referred to as a clinical entity in connection with a case reported by Saundby and Russell,¹⁴ in 1903. It was not, however, until the appearance of Osler's papers,¹⁵ in 1903 and 1904, that the condition was brought prominently before the profession in this country and its existence established.

During the five years which have elapsed since the appearance of Mackey's thesis an increasing number of cases have been reported annually. One hundred and forty-nine apparently unquestionable cases are now on record, which number would undoubtedly be considerably augmented were all the facts known in connection with the thirty additional cases which have been included in the questionable list in the summary at the end of this article.

ETIOLOGY

The cause of the disease is unknown. Rendu and Widal¹⁰ attributed it to primary splenic tuberculosis and considered that the diminished function of the organ caused increased erythroblastic activity of the bone marrow.

Collet and Gallavardin,¹⁶ in 1901, reported a case of "massive primary tuberculosis of the spleen," in which the blood-cells were not counted, but in which the general physical features of the blood were similar to cases of erythremia.

Vaquez,¹⁷ in 1899, Turk,¹⁸ in 1902 and Osler,¹⁹ in 1903, stated their belief that the disease was not due to splenic tuberculosis, but that, on,

10. Rendu and Widal: *Bull. Med. Soc. d. hôp.*, 1899, iii, ser., page 528.

11. Cabot: *Boston Med. and Surg. Jour.*, March 15, 1900, cxlii, 275; and Dec. 7, 1899, cxli, 574.

12. Cominotti: *Wien. Klin. Wchnschr.*, 1900, xiii, No. 39, p. 881.

13. McKeen: *Boston Med. and Surg. Jour.*, June 20, 1901, cxliv, 610.

14. Saundby and Russell: *Lancet*, London, 1902, i, 515; *Brit. Med. Jour.*, 1907, i, 1165.

15. Osler: *Am. Jour. Med. Sc., Phila.*, 1903, N. S., cxxvi, 187-201; *Brit. Med. Jour.*, 1904, i, 121.

16. Collet and Gallavardin: *Arch. de méd. exper. et d'anat. path.*, 1901, xiii, 191.

17. Vaquez: "Hyperglobulie et Splénomégalie," *Bull. Soc. méd. d. hôp., Paris*, June 16, 1899, p. 579.

18. Turk: *Wien. Ges. f. inn. Med.*, 1902.

19. Osler: *Jour. Med. Sc., Phila.*, 1903, N. S., cxxvi, 187-201.

the other hand, it was due to a primary hyperplasia of the erythroblastic bone marrow.

According to Weber,²⁰ objection to the view that the excessive formation of red cells in the bone marrow is the primary condition in erythremia has been urged by Lommel, Bence and others. In several cases of (clinically) splenomegalic polycythemia (erythremia) evidence of local or general blood stasis has been found, suggesting that the polycythemia was secondary. Bence states that the polycythemia in the splenomegalic type can be diminished by oxygen inhalation, but Stern and others obtained negative results by this method.

As having a possible bearing on the etiology of the condition, Weber²⁰ suggests that it may be considered analogous to leukemia, or as a result of a reversion to, or persistence of, fetal and early life conditions in which the bone-marrow is red and still actively engaged in the formation of red cells.

Nervous excitement, mental worry, toxemia originating in the spleen, lungs or alimentary canal, and compensatory reaction towards some hypothetical disturbance in the gas exchanging functions of the blood have all been suggested as possible causes of the disease.²¹

Reckzeh,²² reporting a case of polycythemia occurring in a male of 24, in which there was progressive compression of the superior vena cava by a malignant tumor of the thymus, was inclined to consider stagnation of the blood, from various causes, as the sole cause of erythremia, but Osler²³ does not consider his reasons or experiments convincing, and Behr²⁴ says, "The view that the increase of red cells and the general cyanosis are the result of a simple stasis appears rather forced if we consider that, while such cases of acquired stasis are frequent, yet such cases accompanied by polycythemia are extremely rare."

Anders²⁵ case led him to consider defective venous tone as playing an important rôle in the pathogenesis.

A theory, which has the support of Metchnikoff, assumes that some toxin of a hemolytic nature is manufactured by the enlarged spleen and is absorbed into the circulating blood in minute quantities, not sufficient to cause hemolysis, but sufficient to excite reaction in the blood-forming organs. Belonovsky,²⁶ by injecting minute doses of hemolytic serum into the blood of anemic individuals succeeded not only in raising the number of red corpuscles, but also the amount of hemoglobin.

20. Weber: *Quart. Jour. Med.*, Oxford, January, 1908, ii, 85.

21. Allbutt and Rolleston's *System of Medicine*, 1909, v, 831.

22. Reckzeh: *Ztschr. f. klin. Med.*, 1905, lvii, 215.

23. Osler: *Modern Medicine*, 1908, iv, 678.

24. Behr: *Klin. Monatsbl. f. Augenh.*, 1911, xlix, 672.

25. Anders: *Am. Jour. Med. Sc.*, 1907, N. S. cxxxiii, 829.

26. Belonovsky: *Sur l'Influence de l'injection de diverses doses de serum hemolytique sur le nombre des elements du sang*, St. Petersburg, 1902.

The blood has been examined in several cases for methemoglobin and sulphhemoglobin with negative results.

Age: The disease is comparatively uncommon in early life, only 12 per cent. of the patients being under the age of 30, while 64 per cent. occurred between the ages of 40 and 60.

The two youngest patients were girls, aged 17, one being reported by Chace (Case 58 in summary) and the other by Sandesky (Case 67), and Reissmann (Case 94) and Hann (Case 108) each reported a case occurring in a girl of 18. It is true that Guinon, Rist and Simon (Case 152) reported the case of a girl of 10 years with polycythemia, cyanosis and splenomegaly, but in the case in question there was chronic jaundice and the polycythemia and cyanosis were transitory; it cannot, therefore, be regarded as a case of erythremia.

At the other extreme of life is the case of a female of 68 reported by McQuitty (Case 102).

The cases²⁷ were divided with respect to age as follows:

	Per cent.
Second decade	4
Third decade	8
Fourth decade	18
Fifth decade	37
Sixth decade	27
Seventh decade	6

Sex: Sex has no noteworthy bearing, although the proportion of male to female patients is about two to one. In the 140 cases in which the sex is stated, eighty-nine occurred in males and fifty-one in females.

Occupation: Has no particular bearing beyond the probability that an active life was led by the majority of the patients, judging from those cases in which the occupation is stated.

Race: As the nativity is given in but twenty cases, no satisfactory conclusions can be drawn as to the influence of race on the occurrence of erythremia. In the twenty cases in question ten of the patients were Hebrews, three natives of the United States, two each English and German, and one each Irish, Dutch and Polish. Of the remaining 129 cases sixty-six were reported in German publications, thirteen in the United States, seven in Italy, five in France, four in Hungary and one each in the Philippine Islands and Australia.

SYMPTOMS

Erythremia is characterized by marked, persistent and absolute increase of the red blood corpuscles; marked increase in the viscosity and total volume of the blood; excessive erythroblastic activity of the bone-

27. All statistics given in this article refer only to the 149 cases in Tables A, B, C and D of summary appended, the thirty doubtful cases in Table E not being taken into account.

marrow, and, usually, by characteristic changes in the eye-grounds, cyanosis and enlargement of the spleen.

Weber²⁰ suggests that the sequence of events is probably as follows:

1. Increased erythroblastic activity in the bone-marrow.
2. Increased viscosity of the blood resulting from this polycythemia.
3. Dilatation of the small blood-vessels so as to lessen the resistance to the abnormally viscid blood.
4. Arterial hypertonia as a result of the great strain thrown on the circulatory mechanism.
5. Cyanosis, when it occurs, is probably due to the inadequacy of the series of compensatory changes which precede it.

The physician's advice is usually sought on account of (1) the abnormal color of the skin and mucous membranes (present in 83 per cent. of cases), (2) the symptoms of cerebral congestion, such as headaches (present in 31 per cent. of cases), and vertigo (34.5 per cent. of cases), (3) dyspnea (19.5 per cent. of cases), and (4) lassitude and weakness (19.5 per cent. of cases).

Twenty-three per cent. of the patients complained of hemorrhages, 19 per cent. of pain in the left hypochondrium and 14 per cent. of loss of flesh.

Occasional symptoms were constipation, vomiting, indigestion and palpitation, each in about 10 per cent. of the cases; swelling of the limbs, cough, edema and clubbed fingers, each in about 6 per cent. of cases; and disturbed menses, tinnitus aurium, anorexia, fulness of head, sweating and diarrhea, each in about 4 per cent.

Cyanosis: In 75 per cent. of the cases summarized by me in the tables at the end of this article distinct cyanosis was present, and in about 8 per cent. of the cases it is stated that the patient, while not distinctly cyanosed, was "very red," "florid," "face congested," "plethoric," etc., so that in 83 per cent. of the cases there was some intensification of the color of the skin.

Cyanosis was absent or not reported in 17 per cent. of the cases.

It was one of the first symptoms in 15 per cent. of the patients.

The cyanosis may be general, but is usually more marked in the face and hands. The tongue is nearly always a characteristic bluish red color. The patient may be deeply cyanosed, moderately cyanosed, or there may be merely a florid appearance with great dilatation and engorgement of the superficial vessels. The most common condition appears to be a distinct cyanosis of the face, more marked in the nose, ears, cheeks and lips; duskiness or deep redness of the tongue and mucous membranes; and more or less discoloration of the hands. From this it will be observed that the cyanosis is most common in the exposed portions of the body.

Discoloration of the feet was reported in two cases (5 and 124) and of the trunk in two cases (20 and 69).

Exposure to cold and mental excitement seems to intensify the cyanosis, while a warm room may cause the blue color to give place to red. The symptoms seem to subside somewhat in summer (Case 12).

In a number of cases the patient presented a striking appearance. One of Osler's patients (Case 10) was known as "the blue baby." Aldrich and Crummer's patient (Case 47) was called "the red Indian woman." Other authors spoke of the cyanosis as "extreme," "intense," "startling," "remarkable" and "extraordinary."

Skin, Mucous Membranes, Etc.: Vascular engorgement is usually noted in the buccal and pharyngeal mucous membranes, conjunctivae and the interior of the eye and frequently in the superficial vessels. In 25 per cent. of the cases the veins are described as being distended and the conjunctivae was reported injected in 19 per cent.

In 3 per cent. of the cases slight pigmentation of the skin is reported. Carbuncle, erythema, bronzing, psoriasis and *tâche cérébrale* were each reported in one case.

Osler drew attention to the fact that a white line could be produced by cutaneous irritation, a sign which some French writers supposed to be connected with functional insufficiency of the suprarenals.

Dermatographia and erythromelalgic symptoms have been reported in a few cases.

Lungs: Usually either no mention is made of the lungs or they are reported as being normal. Dyspnea, however, is recorded in 19.5 per cent. of the cases, some degree of emphysema in 8 per cent. and cough in 6 per cent. Asthmatic attacks were reported in three cases and excessive expectoration in two cases.

Heart and Circulatory System: In only a very few cases was the cardiac involvement worthy of consideration. No mention was made of the organ in 28 per cent. of the reports; 30 per cent. report the heart normal; 27 per cent. state that the heart was somewhat enlarged, and 15 per cent. call attention to very slight cardiac irregularities. If, then, a normal heart be assumed in the 28 per cent. of cases in which the organ is not referred to, 58 per cent. of the patients were without demonstrable heart abnormality.

Palpitation was reported in 10 per cent. of the cases, tachycardia in four cases and in one case (94) a pulse-rate of 160.

With reference to disturbances in circulation, the feet and legs were blue, swollen and painful in 9 per cent. of the cases; edema and clubbing of fingers and toes each occurred in 5 per cent; arteriosclerosis, varicose veins, thrombosis, gangrene, hemorrhoids and incurvated nails each in

3 per cent.; phlebitis in two cases; cold extremities in one case. Anemia preceded one case.

Hemorrhages: Hemorrhage seems to have been a very prominent symptom, occurring in about one-fourth of all cases, as follows:

	Cases
Epistaxis	in 10
Gums swollen and bleeding.....	in 12
Cerebral hemorrhage	in 3
Hematemesis	in 6
Hemoptysis	in 2
Melena	in 5
Hematuria	in 2
Menorrhagia	in 2
Mucous hemorrhage	in 1
Miscarriage and severe hemorrhage with relief.....	in 1
Prolonged hemorrhage after extraction of teeth.....	in 1

Epistaxis was very marked in one case (58).

Blood-Pressure: Unfortunately, the blood-pressure was reported in only about 60 per cent. of the cases. In sixty-six reports of cases in which the blood-pressure was taken, twenty-one gave the systolic pressure as below 140, while forty-five reported pressures ranging from 145 to 310, as follows:

	Cases
Blood-pressure 145 to 170	23
Blood-pressure 180 to 200	13
Blood-pressure 210, 235, 240 and 310, each one case.....	4
Blood-pressure 220	3
Blood-pressure 200	2

It is interesting to note that in eight cases in which the authors report an absence of splenic enlargement the systolic blood-pressure was comparatively low—110 to 130 in five cases, 140 in one and 150 in two—whereas in twenty cases making no mention of the spleen (from which it may be assumed that the organ was not enlarged) the blood-pressure appears to have been uniformly high, ranging from 150 to 210 in fourteen cases and in six cases (Cases 130, 132, 135, 138, 139 and 142) being reported as from 220 to 310. From this it would appear that, notwithstanding the comparatively low pressure in the eight cases referred to, the blood-pressure is usually above normal in cases showing no splenomegaly (Geisbock's polycythemia hypertonica).

On the other hand, in thirty-eight cases reporting a distinct splenic enlargement, the blood-pressure was below 150 in twenty cases and only exceeded 200 in two cases (82 and 145).

Spleen: Some enlargement of the spleen was present in about three-fourths of the patients. The organ was not mentioned in 18 per cent. and was not enlarged in 8 per cent.

In the 110 cases in which splenomegaly was reported, forty-six reported marked enlargement, fifty-four slight enlargement as determined

by palpation, seven cases "percussion enlargement" and in three cases enlargement was found at autopsy.

Of the forty-six cases in which there was marked splenic enlargement, twenty-one cases reported the spleen as reaching to the level of the umbilicus and nine as reaching to or below the iliac crest.

It is worthy of note that in one case (120) an accessory spleen was found on exploratory incision and in another case (81), what was thought to be a supernumerary spleen was palpated by the examiner.

Liver: The liver did not show any increase in size in the majority of the cases; about a third of the patients presented a *slight* enlargement of the liver, but not to the extent seen in the spleen. A tremendous enlargement of the liver was present in one case (90), and a marked enlargement in six other cases.

Gastro-Intestinal System: In about half of the patients there was disturbance of the gastro-intestinal system. Vomiting was present in 12 per cent. of the cases, constipation in 11 per cent., indigestion in 9 per cent., diarrhea in 4 per cent., anorexia, jaundice, nausea and thirst each in 3 per cent., and stomatitis, hiccup, eructations and ascites each in one case.

Temperature: The temperature, as a rule, is not affected. Fever was reported in but five cases and subnormal temperature in but three cases.

Generative Organs: There was disturbed menstruation in seven cases, prolapse of the uterus in two cases, atrophy of the uterus in one case and in one case (105) the general condition was worse before commencing of menstruation and after the menopause.

Pain: In over a third of the cases the patient complained of pain in some form, headache being the most constant, occurring in 31 per cent. of all cases. Pain in the left hypochondrium was complained of in 19 per cent., in many cases both headache and pain in the left hypochondrium being present. Pain in the chest was present in four cases; pain in the right hypochondrium and tenderness over the bones each in three cases; cramps in the legs in two cases; and neuritis, neuralgia, precordial pain, lumbar pain, pain in the stomach, pain in fingers and toes, shooting pains in the hands, pain between the shoulders and pains in the joints each in one case.

Nervous System: The nervous system appears to have been affected in many cases. The following symptoms have been reported: Tinnitus aurium (in 5 per cent.), apprehension, nervousness, excitability, delirium, irritability, hypochondriasis, disturbed mentality, insanity, insomnia, minus knee-jerks, muscular atrophy, numbness, choreiform attacks, epileptiform attacks, muscular twitching, shivering, tremor, paralysis.

hemiplegia, aphasia, disturbed speech, paraphasia, "heat in head," "lump in throat," fainting, loss of consciousness, syncopal sensations without loss of consciousness, etc.

Eyes: The eye condition in cases of erythremia is especially noteworthy and a careful ophthalmoscopic examination should be made.

The importance of such an examination does not appear to have been appreciated by most of the authors, the eye being mentioned in only forty-four cases (30 per cent.), and an ophthalmoscopic examination having been made in only twenty-six cases (18 per cent.).

White, in reporting a case (Case 119), says: "Judging from the appearance of the fundus oculi, I should say that the condition would always be easy to recognize."

According to Holloway,²⁸ on the other hand, the fundus picture in erythremia cannot be distinguished from the changes produced by congenital heart disease with cyanosis, except that, in his opinion, the congenital cases as a group would tend to show more extensive intraocular changes than would cases of erythremia.

Behr, in writing on this point, says:²⁴

It must be of great importance for the conception of the symptom-picture if we can establish the specificity of the disease by some special symptom which is only found in primary erythrocytosis but never in simple chronic stasis without polycythemia. By its establishment in the so-called secondary cases we can then remove the principal difference between the idiopathic and symptomatic erythrocytoses. Such a symptom we possess in the characteristic changes in the fundus of the eye.

Disturbances of vision were reported in thirteen cases, Hutchinson and Miller's patient (Case 34) becoming quite blind, although nothing was found in the optic disks beyond a slight hyperemia and engorgement.

The conjunctiva is usually injected and in those cases in which an ophthalmoscopic examination was made the retinal veins are almost universally reported as being dark colored and dilated and frequently tortuous.

Parker and Slocum's patient (Case 78) had blurring of vision and occasional diplopia; the veins of the fundus were markedly tortuous and dilated and the retina edematous and deeper red than normal.

The same authors reported a second patient (Case 79) entering the ophthalmologic clinic complaining of severe frontal headache, blurring of vision and diplopia. Examination revealed vision O/D 6/7.5, O/S 6/9, retina hyperemic, veins much engorged, tortuous and dark in color.

Hall's patient (Case 86) was carefully examined by Jackson²⁹ on a number of occasions during a period of two years, the results being set forth in detail in an excellent article accompanied by a plate showing the appearance of the fundus oculi. This patient when first seen by

28. Holloway: New York Med. Jour., Jan. 13, 1912, xcv, 69.

29. Jackson: Ophthalmology, Milwaukee, 1907, iv, No. 1.

Jackson showed an indefinite blurring of vision, epiphora, dilatation of the retinal veins, decreased vision unimproved by any lens, and a slight rotary nystagmus. Later the pupils became unequal and the vision still less and the sinus of the left nerve became markedly larger and distinctly bluish towards the periphery. The appearance was, Jackson says, "distinct from anything I have ever seen."

There was a "considerable blurring of the optic disks, obviously due to edema," in the patient reported by Russell (Case 99). The right disk showed enlarged and tortuous veins and the arteries were also enlarged. The outer part of the disk showed a remarkable group of small arterioles and enlarged vessels were scattered about the retina. Near the macula was a small patch of pigment, "the result of former chorioiditis." The left disk showed a similar appearance to a lesser degree.

Hemorrhagic glaucoma was reported in one of Geisbock's patients (129).

Double optic neuritis was present in three cases (14, 30, 124).

Choked Disk: It will be observed from the foregoing that optic disturbance was present in a number of cases. In only two instances, however—Pfeiffer's case (101) and the author's first case (124)—has choked disk been observed. Behr,²⁴ in a paper published in 1911, goes very fully into the eye condition in Pfeiffer's patient and says:

In the characteristic changes in the fundus we possess a special symptom of marked diagnostic value, and it is to be regretted that only in a very small fraction of the cases reported was the eye examined. All of the cases reported agree that the veins are much dilated and serpentine and dark colored. The arteries are either normal, or in rare cases also dilated and darker than normal. Frequently the retina is livid blue. As a rule the margin of the papilla is distinct, rarely indistinct and never with bulging of the papilla itself. That the blood-vessels of the conjunctiva are affected is clear.

Dr. William T. Shoemaker, of the Pennsylvania Hospital, Philadelphia, made a very careful examination of the eye grounds in the author's first case (124) and exhibited the patient before the eye section at the College of Physicians. I am indebted to Dr. Shoemaker for permission to quote from his report as follows:

Special interest from an ophthalmic standpoint lies in the *violent* changes in the optic nerve, retina and blood-vessels. These changes are those of typical inflammatory choked disk, identical, it would seem, with those frequently seen with intracranial disturbance.

Carl Behr,²⁴ in a most important communication on this subject last year, including a case with microscopic examination, says that his case of polycythemia was the first observed with typical choked disk, and, while referring to a number of cases of cyanosis in which optic neuritis, blurring of the disk margins, etc., were noted (Hirschberg, Posey, Harms), he is inclined to think that the changes in these cases were not inflammatory but were due to edema, and, in the absence of swelling, represented perhaps the beginning stage of the more pronounced condition.

The retinal changes which Behr demonstrated from his case are enlargement of the veins with no other alteration in the vessel walls than loss of elasticity and thinning. The retinal capillaries showed general distention and irregularity with fusiform dilatations. All of the veins were filled with red cells, but Schlemm's canal, on the other hand, showed no enlargement and contained but a limited number of red cells. There was a general round cell infiltration. The chorioidal vessels were greatly distended and in pronounced cases the sclera may be of a decided bluish color.

Whether or not the case shows simple edema around the nerve head or pronounced choked disk, as in Behr's case (No. 101) or in the case which I show (No. 124) depends, according to Behr, entirely on the equilibrium maintained in the eyes between the fluid thrown from the blood into the tissues and those carried off through the ordinary lymph channels.

The choked disk in polycythemia, Behr concludes, originates solely from local edema of the papilla and the peripheral end of the optic nerve, and, he states, this choked disk is in no way different ophthalmoscopically and microscopically from that of intracranial origin.

Swan³⁰ claims that one of the prominent symptoms of polycythemia is exophthalmos. In the cases covered by my summary, however, this symptom was reported in only two instances (Cases 78 and 94).

Urine: In a majority of the cases the urine showed a small amount of albumin and not infrequently tube casts. In fifty-two cases the urine is not mentioned; in sixteen it was negative or normal; in eighty cases it presented abnormal features as follows:

	Cases
Trace of albumin	61
Marked albuminuria	8
Tube casts	29
Excess of urobilin	7
Excess of indican	6
Chronic nephritis	4
Sugar	2
Blood	2
Red cells	2
Polyuria	2
Oliguria	1

In addition to the above, urochrome, diacetic acid, acetone, much chromogen, excess of uric acid, leukocytes, diazo reaction (Case 64), eight times the normal amount of iron (Case 113) and a specific gravity of 1,040 were each reported in one case.

Glandular System: The glandular system appears to have been affected in only six cases. The submaxillary glands were enlarged in one case, the mediastinal glands in one case (124) and the thyroid gland in four cases (25, 31, 63 and 102).

BLOOD

Red Cells: The most important and constant feature of erythremia is the uniform, absolute and persistent increase in the number of erythrocytes in the circulating blood. This increase varies markedly in different patients and in the same patient at different times.

30. Swan: Internat. Clinics, Philadelphia, 1907, iv, 114.

In the vast majority of cases the number of red cells reported ranges between six and eleven million, an average of twenty cases being reported in each increase of a million cells from six to eleven millions. That is, twenty cases reported from six to seven millions, twenty cases from seven to eight millions, etc.

The highest recorded counts occurred in Seufert's two cases (63 and 64), which showed 15,000,000 and 15,500,000, respectively. Koester's case (Case 40) showed 13,060,000, and in Gibson and Watson-Wemyss's case (Case 111), 13,250,000 cells were present at one time. Thompson's case (61) exhibited 13,000,000, Myer's case (81) 12,880,000, Englebach and Brown's case (38) 12,584,000. Reckzeh's patient (Case 28) had 12,500,000 red cells, Miller's patient (Case 110) 12,010,000 and four cases (3, 56, 65 and 148) reported counts of 12,000,000, making in all thirteen cases in which counts of twelve million or over occurred.

These higher counts are particularly interesting when one considers Weber's²⁰ statement that samples of blood showing ten million red cells per cubic centimeter, with coagulation prevented, placed in a cylindrical glass, show a corpuscular sediment of over nine-tenths of the whole column, the plasma forming only a thin layer on the surface, whereas normally cells and plasma are about equal.

Hemoglobin: Notwithstanding the high erythrocyte count, the hemoglobin percentage in most cases was estimated as quite low. It seems probable that the hemoglobin is underestimated in many cases, as in some instances the statement is made by the author that the estimated per cent. "is the limit of the scale."

In 111 cases in which the hemoglobin percentage was reported all but four stated the percentage to be 100 or over. These four cases reported 80, 85 and 95 per cent. Sixty-eight cases reported percentages ranging between 100 and 150 and thirty-one cases percentages between 155 and 200. One case reported a percentage of 240 (Case 68).

Color Index: I have estimated the color index in seventy-nine cases, and, as was to be expected from the comparatively low hemoglobin percentage reported, found it to be between 0.45 and 100 in all but ten cases. Of these ten cases six ranged from 1.02 to 1.20 and four from 1.31 to 1.57.

Microcytes and Macrocytes: Were reported in one case (47).

Poikilocytes: Present in three cases (28, 33, 47).

Degenerated Red Cells: Reported in two cases (78 and 79).

Nucleated Red Cells: Nucleated red cells were present to a very limited extent in twenty cases and to a marked degree in two cases (47, 89), in one of these cases being mostly of the megaloblastic type. A few megaloblasts were also present in three other cases (61, 77 and 79).

Polychromasia: A tendency of the red cells to stain a lighter or darker blue, known as polychromasia, and said to be found in chronic anemia,³¹ was present in three cases (Cases 33, 38 and 47). This condition is regarded by Ehrlich as evidence of degeneration, but, on the other hand, some authorities regard such cells as immature and consequently significant of regeneration.

Hemolysis: Resistance to hemolysis was reported as slightly increased in one case.

Color of Blood: Is almost invariably darker than normal.

Viscosity: The viscosity of the blood is invariably raised whenever the number of red cells per c.c. is much increased. In one case it was stated as 10.43 (Case 110). Weber²⁰ found the viscosity of a citrated specimen of the venesection blood in two cases to be more than twice the normal. He says: "Supposing the viscosity of normal human blood to be 5.1 to 5.3 (that is to say, 5.1 to 5.3 times that of water), Lommel found the viscosity to be over 11.0 in two cases of polycythemia with splenomegaly, Bence obtained figures varying from 15.9 to 20.9, and Munzer in another case showed figures varying between 12.0 and 23.0 according to the special form of viscosimeter which he employed. In Löw and Popper's case the viscosity was 10.4 and in Saundby's case 9.4."

Coagulation Time: The blood in erythremia undoubtedly coagulates much more quickly than normal blood.³² In ten cases in which the coagulation time is stated, four (63, 64, 78 and 94) reported coagulation in one minute or less, three (12, 38, 110) a coagulation time of less than four minutes, and three (60, 75, 81) coagulation in from six to ten and a half minutes.

Oxygen Capacity: The oxygen capacity is stated in but four cases, in one instance (35) being diminished, in another (61) being two and a half times normal, in a third (60) being given as 1,480 c.c. with a blood volume of 4,765 c.c., and in the fourth (110) as 3,375 c.c. with a blood volume of 10,200 c.c.

Total Volume: According to Weber³³ the normal individual is estimated to possess 4.6 c.c. of blood per 100 grams of body weight. It is interesting to note that in the eight cases in which the total volume was estimated it very much exceeded the normal.

In Hutchison's two cases (48 and 49) it was greatly increased and in one of his cases reached "the extraordinary figure of 10,750 c.c., or more than three times the normal volume for a patient of same weight."

31. Butler's *Diagnostics of Internal Medicine*. 1908, p. 617.

32. Normally coagulation is said to occur in five minutes, although Coplin (*Manual of Pathology*, 1906, p. 404) states that his personal observations indicate that a considerably longer time is usually required.

33. Weber: *Med. Chir. Tr. London*, 1905, lxxxviii, 191; and *Tr. Med. Soc. London*, 1907, xxx, 369.

In Miller's case (60) it was 4,765 c.c. In Thompson's case (61) it was two and a half to three times the normal. In Acland's case (50) "the total volume of the blood by the carbon monoxid method was about two and a half times the normal." Weber's case (72) exhibited a total volume of 5,600 to 6,000 c.c., while Miller's second case (110) showed a total volume of about 10,200 c.c.

White, in reporting a case (119), states that the total volume was three times the normal for a man of his weight and calls attention to the fact that "the red cells being double the normal, the patient had six times the normal number of red cells and four times the normal hemoglobin. Such blood must have nearly reached a volume which would render circulation very difficult." The specific gravity in this case was given as 1,076.

Cryoscopy: The cryoscopy finding is given in but two cases, being about normal in one (72) and -0.56° in the other (42).

Glycogen Reaction: In one case (73) the glycogen reaction was distinct but not marked.

Molecular Concentration: Stated in one case (39) as -0.56 .

Leukocytes: Assuming that, as Butler³¹ states, the normal variation of leukocytes in health is from five to ten thousand per cubic millimeter, it appears that in 27 per cent. of the patients there was a moderate leukocytosis (10,000 to 20,000) and in 15 per cent. a distinct leukocytosis (over 20,000).

In four cases the white cells are stated as less than 5,000, one case (31) reporting 1,080, which is probably a typographic error.

Differential: The differential count usually shows some increase in the polynuclear cells, this increase being quite marked in three cases (30, 81, 116). McQuitty's case (102), however, showed a marked decrease in the polynuclear cells and a marked increase in the lymphocytes.

The eosinophils were markedly increased in two cases (25, 124), in one of which 20 per cent. was reported, and showed some increase in four other cases (18, 20, 41, 74).

Basophils or Mast Cells: These cells, which, as Butler³¹ states, are found in small numbers in normal blood and more often in leukemia and have as yet no significance, were reported in varying percentages from 0.5 to 4 per cent. in thirteen cases.

Mycocytes: Were present in five cases (76, 77, 79, 90 and 99) in small numbers and in number around 4 per cent. in three cases (17, 68 and 144). Blumenthal's case (in doubtful list) showed 36 per cent.

OUTCOME OF CASES

According to Osler,²³ Yaquez and Quiserne believed that where the polycythemia reached six million it was fatally progressive.

In thirty-one of the cases, or 21 per cent., the patient died prior to the date of the report. Three of these patients died as a result of splenectomy (Cases 4, 7 and 93), two from tuberculosis, one as a result of secondary hemorrhage following the removal of a uterine fibroid and two as a result of cerebral hemorrhage.

Four of these patients passed into a comatose condition prior to death, three became paralyzed and others suffered variously prior to death from vomiting, diarrhea, aphasia, blindness, dyspnea, mediastinal pain, jaundice and hemorrhages from the stomach and intestines.

Thirteen cases were reported as showing no marked improvement under treatment, while three patients (Cases 8, 21 and 22) were worse after being under treatment over a period of from three to six years.

Two cases (21 and 80) developed thrombophlebitis and one of these patients also developed a pulmonary infarct.

Some improvement was reported as having occurred in twenty-six cases. In eight of these cases the authors state that the polycythemia increased simultaneously with the general improvement. In only two cases (47 and 94) was marked improvement reported.

TREATMENT

With the possible exception of the two cases referred to in the previous paragraph, treatment has been uniformly without permanent benefit.

Splenectomy: In three cases in which the spleen was removed (4, 7, 93) the patients died in from a few days to six weeks later. In the fourth case (161) the patient died seventeen months later of tuberculosis.

Venesection: Venesection is reported as having given temporary relief in seven cases. It was performed nine times in two years in Chamber's patient (56) with marked relief on each occasion, but his patient was discharged "in much the same condition as when she entered the hospital."

Venesection was without result in three cases, while in Fuch's patient (27) there was temporary improvement under treatment by venesection and oxygen.

In my experience venesection has been at all times a helpful method of treatment, but unfortunately gave but temporary relief.

Oxygen: Oxygen was used with some apparent relief in two cases (63 and 64) and was tried without benefit in two cases.

Arsenic: Turk (17), Tooth (103) and Miller (110) reported some improvement under arsenic and Levi's patient (98) "left somewhat improved" after treatment by arsenic combined with Roentgen rays. Arsenic, on the other hand, aggravated the symptoms in Watson-Wemyss's case (112) and was without result in six other cases in which it was tried.

Roentgen Ray: While three cases (33, 47 and 111) showed benefit from the application of the Roentgen rays to the spleen, Case 47 being markedly benefited, this treatment was unsuccessful in six cases.

Faradization: Faradization to the spleen did not materially help Senator's patient (76) and Mackey (Case 42) reports that, while faradization in combination with massage helped the leg weakness, it did not diminish the polycythemia, lessen the cyanosis or prevent gradual enlargement of the liver and spleen.

Diet and Hygiene: In Milchner's patient (113), in whose urine there was eight times the normal amount of iron, a diet containing a minimum of ferruginous material benefited the patient's general condition. Senator (76) by dietetic and hygienic treatment apparently benefited his patient at first but later an albumin-poor diet, with other treatment, was without much effect.

Sodium Nitrite: Osler (Case 9), in referring to a patient who had suffered from headache for four years, states that the headaches were cured by the use of sodium nitrite, but that the patient was under observation for only a few months. Anders (Case 43), in the case of a female of 25, says that the nitrites gave considerable temporary relief from the beginning.

Sodium Bromid: Was used by Koester (40) for pain in splenic region and headache with some apparent benefit.

General: Nicola reports that under symptomatic treatment, tonics and eliminatives, his patient (Case 77) improved and the cyanosis almost disappeared, but the polycythemia was not affected by the treatment, nor by potassium iodid or x-ray.

Carlsbad treatment improved the general condition of Geisbock's patient (Case 31). Inunctions of biniodid of mercury over the spleen, in conjunction with large doses of quinin, resulted in diminution of the size of the spleen and subjective improvement in Begg and Bullmore's case (33), although the polycythemia increased simultaneously with the improvement. Biniodid of mercury was reported as being tried without benefit in three other cases.

Treatment Without Success: Various other therapeutic measures, as follows, were tried without especial benefit by different authors:

Salicylates; tonics; caffeine; bromids; sedatives; nitroglycerin; valerianates; hydrastis; iron (two cases); diuretin; quinin (five cases); colonic irrigations (two cases); digitalis; sodium cacodylate, adrenalin chlorid (two cases); thyroid gland; vinegar (two cases); potassium iodid (four cases).

AUTOPSIES

Autopsies were reported in twenty-three of the cases.

Anemic infarcts were present in the spleen in four cases and yellow nodules in three cases.

There was cirrhosis of the liver in two cases.

The lungs showed the presence of emphysema in four of the autopsies and contained infarcts in two instances. There was bronchiectasis in one case; hydrothorax in one case; old tuberculosis in one case; and tuberculosis of other viscera in one case.

Enlargement of the heart was reported in six autopsies; evidence of old heart disease in two and fibrous myocardium in one.

There was evidence of erythropoietic activity of the bone marrow in ten cases, in most instances the bone marrow being described as red and as having lost its fatty tissue. On the other hand, Saundby and Russell (Case 6) stated that the bone marrow in their case appeared normal macroscopically. In one case Rosengart³⁴ found evidence of leukoblastic and erythroblastic hyperplasia in the liver and spleen.

Softening of the brain and cord was reported in four cases.

DIAGNOSIS

The presence of polycythemia with cyanosis and enlargement of the spleen, and with symptoms of cerebral congestion, such as vertigo, sense of fulness of the head, etc., is suggestive of erythremia, particularly if the eye-grounds show the marked change so often seen in this condition. The absence of demonstrable splenic enlargement or of cyanosis, or even of both, does not necessarily negative the diagnosis. Broadly speaking, in the light of our present knowledge of the disease, erythremia should be borne in mind in all cases of marked *persistent* and *absolute* polycythemia of *unknown origin*.

It should be remembered that the increase in the red cells must be absolute and persistent and the condition must not be confused with the "relative" increase which is due to decrease in the plasma occurring in those diseases accompanied by a rapid removal of fluid from the tissues; e. g., acute diarrhea, dysentery, cholera, etc. Erythremia will be less likely to be confused with relative increase in the red cells if it is borne in mind that in the former condition there is an absence of known cause of diminution in the total volume of the blood. Furthermore, in erythremia, the patients are usually more congested in appearance and the increase in the number of red cells is persistent, whereas in relative polycythemia it is temporary. In erythremia the total volume of blood is above the average; in relative polycythemia it is below the average.

It has been claimed that some degree of local relative polycythemia may be induced by obstructing the venous return, the delay allowing a longer time for the blood to leave the vessels, and, according to Weber,³⁵ impeded circulation may even give rise to general absolute polycythemia.

34. Rosengart: Mitt. a. d. Grenzgeb. d. Med. u. Chir., Jena, 1903, xi, 495.

35. Weber: Proc. Roy. Soc. Med., London, 1908-9. Clin. Sec., p. 24.

Erythremia must also be differentiated from "erythrocytosis," or *secondary* absolute polycythemia, which condition may be regarded as a compensatory reaction of the organism resulting from some interference with oxygenation.

Erythrocytosis is typically seen in congenital heart disease and particularly in congenital pulmonary stenosis; also in chronic diseases of the heart and lungs and in certain individuals residing in high altitudes (Toussy reporting 8,500,000 red cells per cubic millimeter). It has also been reported as a result of chronic acetanilid poisoning (Stengel and White³⁶) and in chronic sulphonal poisoning (Fells) (Case 166).

Both erythrocytosis and erythremia appear to be of myelogenous origin, deficiency of oxygenation in the former causing erythroblastic over-activity of the bone marrow, while in erythremia the increase in red cells is apparently the primary condition, the stimulating factor being unknown.

It is interesting to note that Weil,³⁷ in 1901, found red bone marrow in two cases of congenital pulmonary stenosis and congenital cyanosis, the normal fatty tissue having almost entirely disappeared, and that Mackey, in 1907, confirmed Weil's findings and pointed out that in a case of chronic cyanosis *without polycythemia* he had found *normal* bone marrow.

It has been observed, according to Weber,³⁸ that there is an increased erythropoietic activity of the bone marrow in animals kept at a high altitude or in an artificially rarefied atmosphere. The hemoglobin value as well as the number of red cells is increased and nucleated red cells appear in the circulating blood. On the other hand, animals inhaling an excess of oxygen show a decrease in the number of erythrocytes.

The same author states that other conditions which may give rise to secondary polycythemia (erythrocytosis), by interfering with proper oxygenation, are (1) experimental stenosis of the superior and inferior vena cava, (2) artificial compression of the thorax, (3) diminution of oxygen and increase of carbonic acid gas in the inspired air, (4) clinical or experimental stenosis of the trachea or larynx, and (5) clinical or experimental pneumothorax. According to Weber, Kuhn, by his suction mask (periodical diminution of oxygen pressure in the lungs), was apparently able to produce a decided increase of red cells in some individuals.

An increase in red cells is also seen at times in obesity, paralysis of an extremity, ether anesthesia and phosphorus poisoning.

36. Stengel and White: Univ. Penn. Med. Bull., Phila., 1902-3, xv, 462; Jour. Am. Med. Assn., 1905, xiv, 243.

37. Weil: Compt. rend. Soc. de biol., June 29, 1901, lili, 713.

PROGNOSIS

The disease seems to be progressively but slowly fatal. It has extended in some instances over periods of from ten to fifteen years, but, with the possible exception of two cases (47 and 94), none of the patients so far reported have recovered.

SUMMARY

In the preparation of the accompanying summary of cases reported in the medical literature, said cases have been tabulated as follows:

Class A.—Sixty-nine cases presenting cyanosis and splenomegaly and in which the systolic blood-pressure did not exceed 150.

Class B.—Fourteen cases presenting cyanosis and splenomegaly and in which the systolic blood-pressure exceeded 150.

Class C.—Forty-two cases with an absence of either cyanosis or splenomegaly and in which the systolic blood-pressure did not exceed 150.

Class D.—Twenty-four cases with an absence of either cyanosis or splenomegaly and in which the systolic blood-pressure exceeded 150.

Class E.—Thirty cases considered doubtful.

Class F.—Ten cases the details of which were received too late for inclusion under proper classification.

Making a total of one hundred and eighty-nine cases.

It is difficult, in the light of our present knowledge of the disease, to establish a hard and fast division between cases of polycythemia, probably secondary in form but of obscure origin, on the one hand, and unquestionable cases of primary polycythemia, or erythremia, on the other. It has, therefore, been the endeavor to include in the summary of cases all of those cases of so-called "polycythemia" in which the etiology of the condition presented a reasonable doubt.

Of the thirty cases included in Class E some appear to be identical with a case reported by some other author and such cases are included in the doubtful list in order to avoid duplicating cases in Classes A to D. Others present certain features of erythremia but sufficient details are not given by the authors to permit of a definite classification. Still others fail to present the essential features of erythremia. It is quite probable that some of the cases included in the doubtful class would prove to be true instances of erythremia had all the facts on which the authors based their diagnoses been set forth in their reports.

For purposes of publication it has been necessary to condense the case reports as much as possible but it has been the aim not to omit any essential features from the condensed report.

In conclusion I wish to express my appreciation of the kindness of Dr. Hobart A. Hare in giving permission to report the two cases described herein, as well as for his suggestions and advice in the preparation of this article. I also wish to thank Dr. E. J. G. Beardsley for his encouragement and assistance in many ways.

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TABLE 1 (CLASS A).—(CASES WITH CYANOSIS AND SPLENOMEGALY AND WITH A SYSTOLIC BLOOD-PRESSURE NOT EXCEEDING 150

Case No. and Author*	History	Examination	Blood Examination	Outcome, Treatment, Autopsy and Remarks
1.— Vaquez	Male, aged 40. For ten years dyspepsia, pain in right hypochondrium, cyanosis of the extremities and distention of superficial veins. For three years buzzing in ears, with giddiness, lumbar pain and transient hematuria. At one time gums swollen and bleeding.	General cyanosis. Spleen greatly enlarged. Liver greatly enlarged. Heart normal. Lungs normal. Veins distended. Conjunctive injected.	Red cells over 8,000,000. Hemoglobin 165. White cells normal. Specific gravity 1,080. Color index 1.03.	Patient died following year of acute tuberculosis. Vaquez regarded case as congenital heart disease until autopsy revealed absence of organic heart involvement. Autopsy: Enlarged spleen and liver. Absence of cardiac disease. Spleen weighed 1,800 gm. and liver 2,800 gm. Died with increase of dyspnea. Autopsy: Spleen hard, fibrous and firmly attached by old adhesions to surrounding structures. It contained large caseous areas and weighed 4,000 gm. Tuberculosis present in other viscera. Heart normal. Bone marrow thought to show evidence of over activity.
2.— Rendu and Widal	Male, aged 30. Policeman. Illness began with pain in left hypochondrium. Two years later large, tender swelling same area. Four years later spleen reached to iliac crest. Two years later marked cyanosis of face and extremities.	Marked cyanosis. Spleen reached to iliac crest. Liver somewhat enlarged. Heart normal.	Red cells 6,200,000; later 5,250,000. White cells 4,500. No nucleated red cells.	Four years later skin bronzed and gums spongy and bleeding.
3.—Cabot	Female, aged 50, spinster; American; rubber worker. Otitis at the age of 18. Several attacks of rheumatism. Since menopause at 46, vertigo, palpitation and headache. A year ago constipation, possibly due to lead. Itching at night. Cyanosis of lips for six months.	Cyanosis of face and extremities. Spleen extended to umbilicus. Slight pulmonary systolic murmur. Polyuria; trace of albumin; hyaline casts. Conjunctivæ much injected; retinal veins dark and dilated. <i>Tâche cérébrale</i> marked.	Red cells 12,000,000. Hemoglobin 120. Normoblasts once after venesection. Color index .5.	Spleen removed and patient died of sepsis six weeks later. Note that even with the high blood count before operation the hemoglobin estimated at only 80. Autopsy: In addition to septic changes in the abdomen, caries of spinal column was discovered.
4.— Cominotti	Female, aged 62; single. Father died of spinal caries. Patient has had increasing pain in splenic region for eight years. Attacks of epistaxis since age of 15. Attacks of vertigo and headache for some time.	Cyanosis of face. Spleen enormous and showed fibrous increase. Liver slightly enlarged. Heart normal except apical systolic murmur. Conjunctivæ dirty. Skin pigmented. Submaxillary glands slightly enlarged. Urine shows excess of urobilin.	Red cells before operation 7,500,000; after operation fell to 5,300,000. Hemoglobin 80. White cells 6,000. No normoblasts.	

- 5.—McKeen Male, aged 53; German; packer in iron foundry. For twenty years attacks of dyspnea at intervals. Cyanosis for eighteen months, dating from dyspneic attack. Attacks of vertigo and blurring of vision and sweating every two or three days.
- 6.—Saundby and Russell Male, aged 54; electroplater. Mother died from phthisis. Patient had gastric fever and lues as a young man. At 46 had influenza and spleen reached to umbilicus. Was then well for six years when began have abdominal pain, headache and great muscular weakness with loss of flesh.
- 7.—Van der Weyde and Van Ijzeren Female, aged 44
- 8.—Osler Male, aged 35; Hebrew; tailor. No previous illness. Cyanosed for years. Constipation and vomiting for two years. Later hiccough and pain in left side.
- Extreme cyanosis of face, extremities and tongue, and especially lips, tip of nose, ears, hands and feet. Spleen 2 inches below costal margin. Liver dullness 2 inches below ribs. Lungs emphysematous. Heart sounds clear; pulse tension not high. Gums swollen and bleeding. Eyes congested; retinal veins engorged with dark blood. Fingers slightly clubbed. Urine; trace albumin, blood and granular casts.
- Intense cyanosis face and extremities. Spleen reached to below umbilicus. Liver inch below ribs. Lungs showed impaired resonance and impaired breath sounds at bases. Accentuated pulmonary second sound; pulse regular, full and high tension. Injected conjunctivæ. Clubbed fingers. Mentality poor. Knee-jerks absent. Urine showed cloud of albumin, a few hyaline casts and an excess of indican.
- Chronic cyanosis. Spleen greatly enlarged. Some enlargement of the heart.
- Cyanosis very marked. Spleen not palpable but gave four inches of vertical dullness. Blood-pressure 125. Urine showed trace of albumin and a few granular casts.
- Red cells 9,380,000 to 9,840,000. Hemoglobin 120 plus. White cells 9,600. Polynuclears 74 per cent.; small lymphocytes 18 per cent.; large lymphocytes 6 per cent.; eosinophils 2 per cent. Color index: 0.6.
- Red cells 7,000,000 to 9,000,000. Hemoglobin 140. White cells normal. Color index 0.87.
- Red cells 7,600,000. Hemoglobin 90-95. White cells 12,800. Polynuclear neutrophils 84.7 per cent. No methemoglobin. Color index 0.6.
- Red cells 6,500,000 to 10,000,000. Hemoglobin 125. White cells 8,000 to 30,000. Differential normal. Specific gravity 1,068 to 1,080. Coagulation time 1½ minutes. Color index .63 to .96.
- No treatment or outcome mentioned.
- Patient died soon after, comatose, jaundiced and more cyanosed. Russell saw this patient with enlarged spleen several years before any cyanosis was observed. Autopsy: Spleen 1.361 gm.; appeared normal on section. Considerable mucopurulent secretion in bronchial tubes. Heart somewhat enlarged; left ventricle thickened; evidence of some old mitral disease. Viscera congested. Marrow of femur appeared normal macroscopically.
- Splenectomy performed and patient died twenty-five days later. Note low hemoglobin estimation. Autopsy: Spleen undergoing fibrosis. Veins of portal circulation greatly dilated. Portal vein thrombosed. Hepaticoduodenal ligament thickened from old inflammation. Kidneys normal. After being under observation and treatment for three years seemed rather worse.

*For references see text.

TABLE 1.—(Continued)

Case No. and Author*	History	Examination	Blood Examination	Outcome, Treatment, Autopsy and Remarks
9.—Osler	Female, aged 44. Previously healthy. Has two healthy children. Cyanosis for many years. Headache and failing vision for past four years.	Marked general cyanosis. Spleen 3 inches below costal margin. Liver, lungs and heart normal. Pulse high tension. Urine showed trace of albumin and a few hyaline and granular casts.	Red cells 11,616,000. Hemoglobin 120. White cells 5,000. Specific gravity 1.067. Color index 0.5.	Patient under observation for only a few months. Headaches cured by sodium nitrite.
10.—Osler	Male, aged 46; shoemaker. For 20 years slight cough and pains in chest. For six years failing strength. Cyanosis for four years. Pains in abdomen and legs and occasional attacks of dyspnea for three years.	Very marked cyanosis. Spleen not felt but moderately enlarged at autopsy. Liver 2 inches below costal margin. Lungs emphysematous. Heart enlarged. Veins full. Vessels of fundus oculi congested and tortuous. Skin pigmented. Urine shows trace of albumin.	Red cells 8,250,000. White cells 8,300. Differential normal.	The cyanosis rivalled that of congenital heart disease, the patient being known as "the blue baby." Patient died with drowsiness and collapse. Autopsy: Spleen moderately enlarged. Lungs somewhat emphysematous. Heart about normal. Full notes not available.
11.—Rosen-gart	Male, aged 41. Pain in stomach, vomiting, giddiness, weakness, wasting and dyspnea on exertion. Enlargement of spleen noted four years ago after an attack of measles.	Well marked cyanosis. Greatly enlarged spleen. Liver moderately enlarged. Lungs normal. Heart enlarged and shows systolic murmur. Blood-pressure increased.	Red cells 10,000,000. Hemoglobin 190. White cells 12,000. Specific gravity 1.072. Blood dark and viscid. Color index 0.95.
12.—Col-lins	Female, aged 24; Irish; servant. Three years ago began to have pain in the left side, cyanosis, giddiness, constipation and occasional headache, vomiting and epistaxis. Six months ago left foot blue and swollen for a fortnight. Symptoms subsided somewhat in summer. Menses normal.	Startling cyanosis of face and extremities. Spleen extends from 2 inches below axilla to within 3 inches of iliac crest. Liver not enlarged. Lungs normal, but dyspnea on exertion. Heart normal. Pulse high tension. Conjunctivæ injected. Some pigmentation of skin. Urine normal.	Red cells about 10,000,000. Hemoglobin 110. White cells 17,800. Differential normal. Blood dark and flows slowly, coagulating in less than four minutes. Color index 0.55.
13.—Turk	Female, aged 45; Polish Jewess. Patient at age of chloracetic.	Extraordinary cyanosis. Spleen considerably enlarged. Lungs normal. Heart normal except accentuated aortic second sound. Veins prominent and arteries thickened. Conjunctivæ injected.	Red cells 9,965,000. Hemoglobin 140. White cells 33,800. Blood very dark and viscid. Color index 0.7.	Hall's case (number 163) is possibly a duplication of this case.
14.—Turk	Female, aged 43; laundress. No hereditary taint. Five children. Erysipelas three years ago. Phlebitis of left leg five months ago. Attack of headache and giddiness with right facial paralysis a month ago.	Extraordinary cyanosis. Spleen enlarged. Heart hypertrophied. Veins distended. Double neuro-retinitis. Urine shows cloud of albumin and epithelial and other casts.	Red cells 7,500,000. Hemoglobin 112. Color index 0.75.	Patient died a few weeks later, comatose, with failing heart and edema of the lungs. Autopsy: Spleen enlarged and showed multiple anemic infarcts. All viscera engorged with dark blood. Marked parenchymatous nephritis and hypertrophy of left ventricle.

- 15.—Turk Female, aged 60. Two years ago laid up for five months with pain, swelling and blueness of right foot. Since then has had a similar condition of left foot and right hand.
- 16.—Turk Male, aged 44; weaver. Ten years ago pain in left hypochondrium, fever, wasting and enlarged spleen. Four years ago similar illness. Recovered both times after taking quinin but for some months past complained of pain in left hypochondrium and general weakness.
- 17.—Turk Female, aged 33. Three years ago began to have pain in left hypochondrium and soon afterwards spleen found to be enlarged.
- 18.—Preiss Male, aged 49. Painless enlargement of spleen for seven years. Erysipelas right arm three and a half years ago, followed by thrombosis left iliac vein. Palpitation and dyspnea for past year.
- 19.—Breuer Female, aged 50. For some years attacks of indigestion and faintness with marked cyanosis of skin and mucous membranes.
- General cyanosis. Spleen reaches inches below umbilicus. Liver slightly enlarged. Slight bronchitis and emphysema. Heart slightly enlarged. Distended capillaries; vessels thickened. Conjunctivæ injected. Urine shows cloud of albumin and a few hyaline casts.
- Cyanosis of face. Spleen reaches 2 inches below umbilicus. Liver reaches to umbilicus. Lungs normal. Heart normal. Distended veins. Blood-pressure 115. Conjunctivæ injected. Urine shows albumin but no casts.
- Cyanosis of face and mucous membranes. Spleen to within 2 inches of the symphysis pubis. Liver slightly enlarged. Lungs normal. Heart normal. Distention small veins; vessels soft. Conjunctivæ injected. Urine normal.
- Marked cyanosis face and extremities. Spleen markedly enlarged. Liver markedly enlarged. Slight bronchitis. Heart not enlarged but slight systolic murmur at apex and accentuated aortic second sound. Urine shows a slight albuminuria and a few hyaline and epithelial casts.
- Marked cyanosis. Spleen enlarged. Liver enlarged. Some hypertrophy of heart. Urine shows trace of albumin and occasionally casts and blood.
- Red cells 8,220,000 to 10,630,000. Hemoglobin 180. White cells 12,000 to 19,000. Some excess of polymorphs and a very few nucleated reds. (Color index 0.9).
- Red cells 8,430,000 to 9,670,000. White cells 26,700. Polymorphs somewhat increased. A very few nucleated red cells. Mast cells somewhat increased. Sp. gr. 1.070.
- Red cells 8,380,000 to 9,420,000. White cells 16,000 to 30,000. Excess of polymorphs. Nucleated red cells very rare.
- Red cells about 7,000,000. Hemoglobin 120 to 150. White cells 16,000 to 26,000. Relative increase polymorphs and mast cells. A few nucleated reds. Sp. gr. 1.068.
- Large uterine fibroid removed and patient died of secondary hemorrhage following operation. Autopsy: Spleen showed marked excess eosinophilous cells but no erythroblasts. Bone marrow in state hemopoietic over activity. All viscera engorged. Peritoneal cavity contained large quantity of blood.

*For references see text.

TABLE 1.—(Continued)

Case No. and Author	History	Examination	Blood Examination	Outcome, Treatment, Autopsy and Remarks
20.— Vaquez and Laubrey	Male, aged 60. Otitis at 21. Malaria at 23. At 40 cough, hemoptysis and loss of weight subsiding after two years. Since 50 liable to attacks of giddiness, fainting and vomiting. Last six years pain in left hypochondrium, with dyspepsia and constipation.	Marked cyanosis of face, hands and chest above nipple level. Spleen extends below umbilicus. Liver normal. Heart normal. Some edema of left chest wall. Conjunctivae injected. Mentality slow. Urine shows trace of albumin.	Reds about 8,000,000. Hemoglobin 160-180. White cells 14,000. Relative increase of polys. and eosinoph. A few nucleated reds. Resistance hemolysis slightly diminished. Color index 1.00 to 1.12.
21.—Weintraud	Male, aged 31. Measles and typhoid in childhood. From 18 to 20 paroxysmal pain in abdomen and chest, urine being dark brownish red after each paroxysm. For 17 years liable to frequent migraine-like attacks, recently more severe and associated with parapsasia and enlargement of spleen. At 29 more abdominal pain, spleen larger and albumin in urine. At 31 examined account of swelling of feet.	Cyanosis of face. Spleen reaches to within 2 inches of iliac crest. Liver 2 inches below costal margin. Lungs normal. Heart normal. Urine shows cloud of albumin but no casts.	Red cells over 8,000,000. Hemoglobin 110. Six years later red cells 7,880,000. Hemoglobin 130. White cells 13,000. Relative increase of polys., nucleated reds rare. Sp. gr. 1.057. Color index 0.69 to 0.81.	Two years later thrombo-phlebitis left leg and signs infarct in lung. Six years after first examination edema with distention veins both legs, arteries rigid, conjunctivae injected, cloud albumin in urine; also red cells and casts. Recently patient tapped three times for ascites.
22.—Weintraud	Male, aged 46. Syphilis at 19. Diphtheria at 29. Remained well until four years ago when he began to have daily attacks of headache with giddiness, vomiting and disturbance of vision and right hand became congested and swollen.	Marked cyanosis of face. Spleen reached below umbilicus. Liver, lungs and heart normal. Right pulse much smaller than left but nothing in chest to account for difference. Urine shows albumin but no casts.	Red cells nearly 10,000,000. White cells 30,000. Polys. relatively increased. A very few nucleated reds.	Present condition (four years later) the same except that spleen is larger.
23.—Zambrescu	Female, aged 26. Complained of cough, dyspnea, palpitation and pain in hypochondrium.	Cyanosis of face and extremities. Spleen enlarged. Subcrepitant rales at base of lungs; prolonged expiration; sibilant rales over rest of lungs. Heart rapid. Urine decreased in quantity; two gm. albumin to the liter.	Red cells 7,200,000. Hemoglobin 105. White cells 10,100 No nucleated red cells. Differential normal. Color index 0.73.
24.— Hoehaus	Female, aged 43. Severe pain in left hypochondrium five years ago and again 18 months ago, when noticed large swelling in left hypochondrium.	Marked cyanosis face and extremities. Spleen enlarged and hard. Liver enlarged and hard. Lungs and heart normal. Pulse full and strong. Urine shows albumin but no casts.	Red cells greatly increased. Hemoglobin 170. White cells normal.

- 25.—
Ascoli
Male, aged 20; carpenter. Malaria at age of 8. At age of 15 epigastric and precordial pain and dyspnea. At 18 severe and prolonged febrile attack with violent delirium, excessive sweating, thirst and intense redness of face and neck. Attack left him very weak and subject to severe pain in the epigastrium.
Male, aged 59; porter. For four years headache, disturbed sleep, palpitation and dyspnea. A few weeks ago had diarrhea.
- 26.—
Kraus
General cyanosis, most marked in face and extremities. Spleen considerably enlarged. Liver slightly enlarged. Heart enlarged. Blood-pressure normal. Urine shows albumin and a few hyaline and granular casts.
- 27.—
Fuchs
Cyanosis of face, extremities, tongue and mucous membrane of mouth. Spleen and liver enlarged. Urine shows albumin.
In 1899: Face cyanosed. Spleen to iliac crest. Lungs and heart normal. Urine showed trace of albumin but no casts. In 1902: Still very cyanosed. Spleen to within 1½ inches of pubis. Urine 700 to 3,000 c.c. daily; Sp. Gr. 1.010-1.018.
- 28.—
Reekzeh
Male, aged 42. Only a short society report; no history. Marked symptoms are cyanosis, headache, vertigo and bloody stools.
Male, aged 34. Mother died of tuberculosis. Prior to 1894 patient had measles, scarlet fever, otitis media, meningitis, pneumonia (twice), sciatica, inflammation of left shoulder, catarrh of lungs, gonorrhea and syphilis. In 1896 hematemesis, and soon afterward began to suffer from headache, giddiness, lassitude, and pain under left costal arch.
Male, aged 32. For years liable to headache, colds in head, sore eyes, rheumatic pains and bleeding from nose and gums on slightest provocation. When first seen complained of intense pain in left hypochondrium due to enlarged and tender spleen.
- 29.—
Zimlick
When first seen: Moderate cyanosis of face and hands. Spleen large and tender. Lungs and heart normal. Urine showed albumin but no casts. A few weeks later: Patient became depressed. Cyanosis increased. Transient edema right arm and hand. Liver moderately enlarged; heart somewhat dilated. Albumin and hyaline casts.
- Red cells 7,200,000. Hemoglobin 95. White cells 15,000. No nucleated reds. Eosinophils 20 per cent. Color index 0.66.
Patient improved while in hospital. On one occasion radial blood showed 6,100,000 red cells while capillary blood from ear showed 6,000,000. Comparison with other cases suggested to Weber a toxemic factor in this case.
- Red cells 10,800,000. Hemoglobin 120. White cells 10,200. Blood almost black. Sp. gr. 1.071. Viscosity increased. No nucleated reds. Differential about normal. Color index 0.55.
Red cells increased but number not stated.
Venesection and inhalations of oxygen gave temporary improvement.
- Red cells varied from 8,300,000 in March, 1899, to 12,500,000 four weeks later, dropping to 6,500,000 three years later. Hemoglobin 150; three years later 125. White cells averaged 24,000. Sp. gr. 1.080. Blood from ear almost black. A few poikilocytes.
Red cells about 9,000,000. Hemoglobin 120. White cells 13,000 to 20,000. Relative increase of polys. Color index 0.66.
Soon after last examination patient fell to the floor unconscious, left side being paralyzed and died the following day. No autopsy.

*For references see text.

TABLE I.—(Continued)

Case No. and Author	History	Examination	Blood Examination	Outcome, Treatment, Autopsy and Remarks
30.—Purves Stewart	Female, aged 53. Five years ago headache, vomiting and giddiness with marked weakness of extremities, attack lasting a week. Three years ago similar attack, lasting six months and leaving her permanently weak and unable to work. A year ago pain, redness and swelling left side of abdomen. Pain passed off and did not return. Five weeks ago intense headache, dimness of vision (more marked in right eye) and vomiting without reference to food. Occasionally blood in vomitus. Considerable loss of weight during five years.	Lips cyanosed; face flushed, with dilated veins; tongue and buccal mucosa bright red; hands and feet always warm and persistently flushed; numerous bright red nevoid elevations over trunk. Spleen two inches below umbilicus. Liver enlarged. Accretuation aortic second sound; pulse high tension; arteries thickened; veins of abdomen markedly dilated and tortuous. Skin dry. Double optic neuritis with retinal hemorrhages. Urine, Sp. Gr. 1.024 laden with albumin and showing granular, hyaline and cell casts. Face somewhat cyanosed. Spleen enlarged. Liver enlarged. Lungs and heart normal. Blood-pressure 100 to 110. Slight goiter. Urine showed occasional traces of albumin and a few tube-casts.	Red cells 8,750,000 to 10,000,000. Hemoglobin 130. White cells 24,000. Polys. 94 per cent. Monomorphs. 6 per cent. Blood very dark and viscid. Color index 0.65 to 0.74.	Patient after leaving hospital had an attack of right hemiplegia with aphasia, apparently having a cerebral hemorrhage. Gradually became totally blind in both eyes. Aphasia passed off but hemiplegia persisted. Died soon after (about five months after first seen by Stewart). No autopsy could be obtained.
31.—Geisbock	Male, aged 51. Apparent recovery from severe jaundice; then headache, giddiness and loss of appetite and weight.	Face somewhat cyanosed. Spleen enlarged. Liver enlarged. Lungs and heart normal. Blood-pressure 100 to 110. Slight goiter. Urine showed occasional traces of albumin and a few tube-casts.	Red cells 9,000,000. Hemoglobin 200. White cells only 1,080 (possibly a typographic error). Color index 1.11.	Venesection of 260 c.c., scarcely relieved headache, nor did application Roentgen rays to spleen improve general condition. Carlsbad treatment had a better effect. Geisbock thought this case resembled some of those described by Turk.
32.—Minnowski	Male, aged 22. Remarkably cyanotic from early childhood. Came under observation for cyst in capsule of right kidney which was operated on successfully.	Remarkably cyanotic. Spleen enlarged. No heart disease.	Polycythemia present.	
33.—Begg, Bulmore and Horder	Female, aged 47. Phtisical family history. Always suffered from constipation and migraine-like attacks. Liable to epistaxis. Complaints of swelling in left abdomen, languor and loss of weight.	Marked cyanosis of face and hands. Spleen extends 2 inches below umbilicus. Liver not enlarged. Lungs and heart normal. Varicose veins of legs. Urine normal.	Red cells 6,850,000. Hemoglobin 100. White cells 11,300. Polys. 77.3 per cent. A few nucleated reds. No myelocytes. About four normoblasts to the thousand white cells. Sp. gr. 1.054. Well marked poikilocytosis and polychromatophilia. Color index—0.73.	Injections biniodid mercury over spleen (part being exposed to artificial heat) and large doses quinin resulted in diminished size spleen and subjective improvement. Later good results from Roentgen rays to spleen. Polycythemia, however, increased simultaneously with general improvement (compare with Hann's case—Case 108).

34.—Male, aged 45; farm laborer. Seven years ago fit with unconsciousness; 3½ years ago carbuncle. Six months ago stomatitis, dyspepsia and constipation followed by vomiting, giddiness and loss of weight. A few weeks later spleen enlarged. Lately hematemesis, increased giddiness and twitching of face. Patient finally became quite blind but nothing found in optic disks beyond slight hyperemia and engorgement.

Cyanosis of face; lips and nose deep purple. Spleen reached to umbilicus. Liver not enlarged. Lungs normal. Heart displaced upwards but sounds clear. Vessels thickened. Blood-pressure 145. Gums swollen and bleeding. Optic disks show slight hyperemia and engorgement. Urine shows trace of albumin.

Red cells 8,000,000 to 11,000,000. Hemoglobin 120. White cells 17,000 to 22,000. Relative excess of polys. No nucleated reds. Viscosity increased. Color index 0.54 to 0.75.

Seven years and two months after first attack patient died in coma with hyperpyrexia. Autopsy: Spleen 38 ounces; hard and irregular; many yellow areas resembling infarcts but no tubercles. Dense adhesions between liver, spleen and diaphragm. Heart 12½ ounces; valves normal; myocardium fibrous. Intense congestion everywhere. Left lenticular nucleus and right optic thalamus red and disintegrated. Bone marrow red and microscopically showed changes suggestive of erythroblastic activity.

35.—Male, aged 42; bricklayer. Three years ago began suddenly to have pain in abdomen, headache and giddiness. A month later face became very red and has remained so. Abdominal pain has grown steadily worse.

Red cells 8,300,000 to 8,600,000. Hemoglobin 140. White cells 11,000. Differential normal. Nucleated red cells very rare. Blood very dark and viscosity increased. Oxygen capacity diminished. Specific gravity 1.068. Color index 0.83.

Patient died six months later after developing severe abdominal pain, rapid loss of weight, jaundice and, finally, profuse hemorrhage of stomach and intestines. Venesection had been repeatedly performed (150 to 200 c.c.) with temporary subjective relief. Autopsy: Spleen adherent and contained scattered yellow nodules. Liver smooth; ante-mortem thrombi in portal system; hepaticoduodenal ligament converted into venous angioma. Lungs congested. Heart slightly enlarged. Stomach and intestines contained dark fluid blood; mucosa blue and swollen. Bone marrow had lost fat cells.

36.—Male, aged 44; shoemaker. Syphilis at 24. Pain in left abdomen for fourteen years. Headache for seven years. Redness of face two years. Pain and swelling in legs for four months. Lately anorexia and constipation.

Red cells 10,000,000 to 11,500,000. Hemoglobin 90. White cells 7,000. Differential normal. No nucleated reds. Viscosity much increased. Color index 0.39 to 0.45.

Patient died shortly after examination with paralysis of right side and great dyspnea. Autopsy: Spleen showed scattered yellow patches of ischemia. Lungs congested, showing several infarcts. Heart dilated and hypertrophied. Bone marrow showed dark bluish red areas of erythroblastic tissue replacing fat cells. Brain congested and edematous; cord degenerated.

*For references see text.

TABLE 1.—(Continued)

Case No. and Author*	History	Examination	Blood Examination	Outcome, Treatment, Autopsy and Remarks
37.— Schm- linsky	Male, aged 42. Has had pneumonia. Two years ago pyelitis. Since then face has become dark red. Complains of dyspepsia, constipation, erythromelalgic symptoms, loss of flesh, general weakness and vertigo.	Cyanosis of face. Spleen enlarged. Liver much enlarged. Cutaneous veins dilated. Veins of fundus oculi dilated.	Red cells 10,800,000. Hemoglobin 160. White cells 12,800. Polys. 81.7 per cent.; large mono. 4.2 per cent.; small mono. 3.8 per cent.; eosino. 3.6 per cent. No nucleated reds; no polkilocytes. Color index 0.74.
38.— Engle- bach and Brown	Female, aged 40; Russian Jewess; housewife. For ten years chronic headache, vertigo and diffuse redness of skin. Five years ago "sudden rush of blood to head," extreme vertigo and excruciating headache, the attack lasting one minute and succeeded by syncopal sensation without unconsciousness and followed by general weakness. At about this time lump appeared in side. Three years ago, following extraction of teeth, had prolonged hemorrhage and severe cramps in legs. Two years ago abdominal pain, headache, anorexia and menstrual disturbances.	Mild diffuse cyanosis; lips purplish, tongue red and gums and mucosae dusky red; toes slightly cyanosed and cold. Spleen tender on pressure and reaches mid line and to level of umbilicus. Liver finger breadth below costal margin. Lungs normal. Heart somewhat enlarged. Venues dilated. Blood-pressure 135 to 140. Conjunctivae injected. Fundus oculi dark red and veins large and dark blue. Tenderness over sternum and superficial bones and scalp. Hemorrhoids present. Urine shows trace of albumin.	Red cells 8,000,000 to 12,584,000. Hemoglobin 180 to 200. White cells 6,000 to 9,600. Polys. 75 per cent.; large lymph. 3 per cent.; small lymph 11 per cent.; transitional 6 per cent.; mononuclear 5 per cent.; eosinophils 1 to 1½ per cent.; no nucleated reds nor myelocytes. Polychromatophilia present. Coagulation time four minutes. Blood dark red and very thick. Sp. gr. 1.065 to 1.075. Oxyhemoglobin present. Color index 1.00.	Duration eleven years. Treatment entirely without success. Quinin increased vertigo and headache. Salicylates, iron and tonics, calomel, bromids, sedatives, nitroglycerin, valerianates, hydrastis, Fowler's solution, etc., all tried without any special improvement. Three x-ray exposures over spleen, of five minutes duration, produced no change in either symptoms or blood findings. Myer (Bull. St. Louis Med. Soc., Dec. 15, 1910, iv, p. 451), speaking of this case, states that two months prior to patient's death she suffered the most intense pain in the mediastinal region from the cardia to the pharynx; also in extremities. A month prior to her death she was greatly emaciated and unable to take food. Her face was markedly cyanotic up to the last. Senator in his article goes very fully into the findings of a number of blood-examinations, including re-fraction value of serum, amount dry residue, etc.
39.— Senator	Male, aged 40; workman. Father died of tuberculosis; mother of dropsy. Diphtheria in childhood. Six years ago took cold and had fever, cough, expectoration, with some blood (never large hemorrhage), stinging pain in chest and night sweats. Also pain in left abdomen which still persists. Denies venereal infection. Formerly drank much whiskey but not much beer.	Patient strong. Face and mucous membranes dark red. Spleen much enlarged. No fever. Glands not enlarged. Blood-pressure 145. Urine shows a trace of albumin.	Red cells 7,316,000 to 10,200,000. Hemoglobin 122 to 185. White cells 5,600 to 20,500. Polys. 73.8 per cent.; Mononuc. 3.5 per cent.; Lymphocytes 18.8 per cent.; Eosino. 3.5 per cent.; Mast cells 0.5 per cent. A few normoblasts. Viscosity much increased. Molecular concentration 0.56.	

Male, aged 44. In 1904 first noticed that gums bled on slight provocation. Complained of headache, vertigo, constipation, pain in abdomen and darkening of vision (coming on suddenly).

Red cells 13,060,000. White cells 9,800. No abnormal cells in stained preparation.

Cyanosis appeared while under observation. Spleen moderately enlarged. Arteries sclerotic. Urine shows some albumin. Eyes: see "Remarks."

Treatment: normal salt solution and sugar per rectum and sodium bromid for pain in splenic region; headache decreased. Inhalations oxygen given but cyanosis soon developed with headache, vomiting, etc. Treatment continued, however, and patient improved and is again able to work. Jackson (Ophthalmology, Milwaukee, 1907, iv, No. 1) says this case showed some disturbance in retinal circulation causing attacks monocular blurring of vision.

Female, aged 45; washerwoman. For two years cyanosis of face and hands. For one year abdominal pain and anorexia. For past two months attacks of giddiness, vomiting and heaviness of feet.

Well marked cyanosis of face and hands. Spleen 3 inches below costal margin. Liver 3 inches below costal margin. Lungs and heart normal. Pulse high tension. Conjunctivæ injected. Urine normal.

Red cells 7,300,000. Hemoglobin greatly increased. White cells 6,400. Moderate relative increases of eosino. A few nucleated reds. Viscosity greatly increased.

Male, aged 51; English; laborer in iron foundry. Father died of "stroke;" mother of dropsy. Patient drinks beer freely. Three years ago influenza, followed by legs becoming blue, swollen and painful. For two years cyanosis, distended veins, pain and weakness in legs and inability to work. For one year enlarged spleen and liver, edema of legs, abdomen and thoracic wall, and albumin, indican and urobilin in urine. Constipation present.

Two years ago: hemoglobin 170; white cells 4,200 to 13,000. One year ago: red cells over 8,000,000. At present red cells from 6,500,000 to 9,600,000. Polys. 81 per cent.; lymphoc. 15.4 per cent.; hyaline 2.6 per cent.; eosin. 1.0 per cent. Velocity normal. Viscosity increased (visc. 9.4). Blood very dark. Sp. gr. 1.067 to 1.080. Cryoscopy -0.56 deg. C. No nucleated reds. No microcytes or poikilocytes.

Digitalis and squill removed edema. Liquor arsenicalis, quinin sulphate, irrigations of colon with alpha naphthol solution, adrenalin chlorid, thyroid gland, vinegar, K. I., and biniodid of mercury all tried without benefit. Erythrol tetranitrate benefited him but had to be discontinued account giddiness. Massage and faradism helped leg weakness, as did also elastic bandage. Treatment has not diminished polycythemia, lessened cyanosis nor prevented gradual enlargement of spleen and liver.

TABLE 1.—(Continued)

Case No. and Author	History	Examination	Blood Examination	Outcome, Treatment, Autopsy and Remarks
43.— Anders	Female, aged 23; single. Family history of Bright's disease, eczema, rheumatism, moderate obesity, organic heart disease and hemophilia. Personal history of measles and colds. Eyes had since age of 10. Epistaxis 11 to 23. Cyanosis, slowly increasing, first noted at 15. Congestion of lungs at 17. Rheumatism and severe headaches since 17. For several years timid, mentally distressed and apprehensive. For past year headaches better, cyanosis worse, and violent cramps in legs and feet and slight vertigo at intervals. Menstruation, formerly painful, is now irregular.	Face markedly cyanotic except around mouth, chin, base of ears and a narrow border around both eyes; mucous membranes somewhat less livid. Spleen slightly enlarged. Liver not enlarged. Heart rapid (110 to 120); slight enlargement of left ventricle; second aortic sound slightly accentuated. Superficial veins lack tone. Blood-pressure 145. Thyroid normal. Urine usually negative but showed sugar (less than 1 per cent.) on one occasion. Height 5 feet 6 inches. Weight 198½ pounds.	Red cells 5,300,000 to 6,950,000. Hemoglobin 110. White cells 13,600 to 20,000. Mostly polys. Red cells stain normally and are of normal size and form.	Treatment directed toward reestablishment menstrual function. For past two and a half years there have been recurring exacerbations and remissions. Headaches practically absent for over a year, or since menses more nearly normal. Apprehension and cyanosis noticeably improved during last six months and now (Jan., 1907) nervous tremor, apprehension and endurance markedly improved. Nitrites gave considerable temporary relief from headaches from beginning, showing cause of headaches to be, in part, at least, heightened tension in cerebral vessels.
44.— Anders	Male, aged 31; clerk. Indigestion for 15 years. Vision blurred at times. Headaches, mental apprehension and slight dizziness have been chief nervous phenomena. Cyanosis for five years. Easily tired for several years.	Cyanosis of the lips, conjunctive, ears and face and especially the nose; hands and feet also quite dusky. Spleen slightly enlarged. Left ventricle somewhat hypertrophied; faint systolic murmur at apex; second pulmonary sound moderately accentuated. Pulse accelerated; tension not high. Urine negative. Height 5 feet 9 inches. Weight 125 pounds.	Red cells 7,400,000. Hemoglobin 130. White cells 12,600. Polys. 69 per cent.; small lymph. 24 per cent.; large lymph. 6½ per cent.; eosin. 0.5 per cent. No polkilocytes or macrocytes, microcytes or nucleated reds. Red cells uniform diameter, perfect contour and stain well. Color index 0.88.	Digestion improved under treatment, but cyanosis and nervous phenomena not relieved. Digitalis, strychnin and nitrites afforded only temporary relief.
45.—Wes- tenhoffer and Hirsch- feld	Male, aged 28. Supposed to be suffering from meningitis. No blood count made during life but autopsy suggests strongly the existence of polycythemia.	Cyanosis present. Spleen enlarged.	Autopsy: Spleen large, due chiefly to engorgement. Malpighian corpuscles smaller than average; the slight myeloid transformation was leukoblastic, erythroblasts being present only in very small numbers; very few cells containing phagocytes seen. Cerebral hemorrhage but no meningitis; viscera and bone marrow extremely engorged, all cellular elements of marrow increased; white cells more than erythroblasts. Normal fat entirely disappeared. While nucleated reds not relatively in excess, the total number in bone marrow must have been enormously increased.

46.—
Stur-
berg

Male, aged 48; workman. In 1904 received a blow on the head but no unconsciousness or vomiting. Since then headache and later vertigo.

47.—

Aldrich
and
Crum-
mer

Female, aged 53. Mother died of tuberculosis. For eight years patient has had striking redness of face (was called "the red Indian woman"), fullness of head and occasional vertigo. Three years ago noted tumor in abdomen. A year ago complained of dizziness, extreme fatigue, feeling of weight in abdomen and pressure over bladder, slight nausea and occasional diarrhea. No fever or loss of weight.

48 and 49.
Hutchi-
son

Two cases referred to by Weber as having come under the observation of Dr. R. Hutchison at the London Hospital. Weber says they were typical cases of "splenomegalic polycythemia" but gives no details other than as stated under "Blood Examination."

50.—

Acland

Weber says: "I have Dr. Acland's permission to state that in an as yet unpublished case of splenomegalic polycythemia under his care at the St. Thomas Hospital a clinical estimation of the total volume of the blood by the carbon monoxid method was made and that it was about two and a half times the normal."

Cyanosis of face, Spleen enlarged and very firm. Conjunctive injected. Blood-pressure 140 to 145. Moderate albuminuria.

Exposed skin dusky red with enlarged veins. Spleen extends 1 inch to right of umbilicus and down beyond crest of ilium. Liver not enlarged. Lungs slightly emphysematous. Heart normal. Conjunctive injected. Urine negative.

Red cells 6,272,000 to 7,264,000. Hemoglobin 120. White cells 4,860 to 7,300. Neutrophils 73 per cent.; lymphocytes 16 per cent.

Red cells 7,700,000. Hemoglobin 120. White cells 4,700. Polys. 72.5 per cent.; L. lymph. 8.0 per cent.; S. lymph. 11.0 per cent.; eosin. 4.0 per cent.; myelocyt. 4.5 per cent. Many microcytes and a few macrocytes; some poikilocytosis and polychromatosis. Considerable number of nucleated reds (24 in a count of 200 white cells), mostly all of megaloblastic type. Color index 0.78.

Total volume of the blood was greatly increased and in one of these cases it reached "the extraordinary figure of 10,750 c.c., or more than three times the normal amount for a patient of same weight."

See "History."

No treatment mentioned but author thinks that condition was not due to trauma.

Arsenic tried but had to be discontinued. Tumor was regularly given fifteen minutes exposure to Roentgen ray; after eleventh exposure symptoms practically disappeared, tumor being smaller and red cells fell to 6,048,000, hemoglobin to 90, microscopic findings about as before. At present, a year later, no further blood-examinations have been made but report from patient indicates continuing improvement. Aldrich and Crummer call attention to this being one of the few cases showing definite improvement.

Apparently no detailed report has been made of these cases.

Apparently no detailed report has been made of this case.

TABLE 1.—(Continued)

Case No. and Author	History	Examination	Blood Examination	Outcome, Treatment, Autopsy and Remarks
51— Voelcker	Case mentioned by Weber as having been observed by Dr. A. F. Voelcker but which had not yet been published. It is assumed from Weber's reference that this was a typical case, but no details were given.	See "History."	Apparently no detailed report has been made of this case.
52— Cassirer and Ban- berger	Male, aged 39. Of a nervous family. Has worked hard and had much trouble. Is hypochondriacal; feared spinal and brain disease.	Cyanosed. Spleen enlarged. Liver moderately enlarged. Blood-vessels dilated. Temperature always below 98.6 F. No albumin in urine.	Red cells 8,500,000 to 9,600,000. Hemoglobin 130-160. White cells 9,760. A month later red cells 6,150,000.	Patient left sanitarium improved and took up his work. No further examinations.
53— Schupfer	Male, aged 42. Enlarged spleen removed for supposed Banti's disease and progress followed for 3 years. Patient improved in general health and liver, enlarged before operation, returned to normal size, but polycythemia and chronic cyanosis gradually developed.	Chronic cyanosis. Spleen enlarged. Transitory enlargement of liver.	Red cells (on two counts before operation) 2,899,000 to 4,920,000. Three years after operation red cells 6,270,000.
54— Mc- Quitty	Male, aged 46; watchman; formerly policeman. High colored for 20 years. Illness began in June, 1905, with pain in left hypochondrium. Admitted July, 1907, complaining of numbness and lividity of left hand, weakness, loss of flesh and swelling in abdomen. In September, 1907, attack of vomiting and diarrhea with passage of a large amount of blood. Was weak for a few days afterwards but pain between shoulders, headache and giddiness disappeared and did not return while under observation.	Face, tongue and mucous membrane livid red; both hands bluish red. Spleen 4 inches below costal margin. Liver the same. Lungs negative. Heart negative at first but while under observation developed a slight systolic murmur and accentuated aortic second sound. Capillaries dilated; marked tortuosity and thickening left radial artery and visible pulsation large arteries. Pulse of increased tension. Optic fundi normal. Knee-jerks minus. Urine contains albumin.	Red cells 9,400,000. Hemoglobin 162. White cells, 12,100. Polys. 80 per cent.; Eosino, 6 per cent.; Lymph. 3 per cent.; S. lymph. 9 per cent.; Transi. 2 per cent. Color index 0.91.	In January, 1908, was much less cyanotic and heart had developed a murmur at apex; liver and spleen enlarged. Treatment: potassium citrate gr. xx four times daily for ten weeks. During its administration numbness and lividity of the left hand gradually disappeared and the patient felt better, with no recurrence of the vomiting and diarrhea.

- 55.—
Cautley
Male, aged 47. Complains of tender swelling in splenic area.
Face varied from deep red to cyanotic. Spleen enlarged. Albuminuria present.
Red cells 7,500,000 to 10,000,000. Blood extremely viscid.
Death from cerebral hemorrhage. Autopsy: Spleen firmly adherent to surrounding structures and contained two infarcts. Soft splenic tissue divided into lobules by fibrous bands. Cardiac hypertrophy. Granular kidneys. Bone marrow of long bones red. Cautley thinks condition a result of local thrombosis of extremely viscid blood and that microscopic examination of marrow or organs did not afford any indication as to etiology.
- 56.—
Chambers
Female, aged 65. Illness began in 1899 with pains in abdomen, dyspepsia and palpitation following severe strain in lifting. Has had frequent attacks of dyspnea and cyanosis. Venesection nine times in two years with marked relief on each occasion. Admitted Nov. 15, 1906, on account of pain, dyspepsia and palpitation.
- 57.—
Munzer
Male, aged 55. Had suffered from pleurisy for a year before he came under observation.
Plethoric looking but not markedly cyanotic. Spleen distinctly enlarged and tender. Liver just palpable below costal arch. Recent bronchial catarrh. Heart enlarged to right. Pulse 86, full and regular. Respiration 24. Temperature subnormal. Patient well nourished.
Red cells 6,660,000. Later 7,800,000. Had been as high as 12,000,000 at one time. Hemoglobin at present 105.
Venesection nine times in two years, in amounts from 20 to 25 ounces, with marked relief on each occasion. Patient was discharged in three months in much the same condition as when admitted to hospital.
Treatment dietetic. Patient left improved.
- Red cells 7,000,000. Hemoglobin, Sahli, 135; Fleischl, 140. White cells 20,000. Color index 1.00.
- Cyanosis of face. Spleen greatly enlarged. Liver somewhat enlarged. Urine contains much albumin.

*For references see text.

TABLE 1.—(Continued)

Case No. and Author*	History	Examination	Blood Examination	Outcome, Treatment, Autopsy and Remarks
58.— Chace	Female, aged 17; school-girl. Except for measles in childhood, health has always been good. Has never menstruated. Three years ago confined to house with severe cough. Since then palpitation, hoarseness, general weakness, blueness of lips and fingers and irritable disposition. Three months ago fainting spell, preceded by distinct aura consisting of groaning and twitching of muscles of forehead. Consciousness lost for about five minutes and on awaking found bed clothes saturated with blood from nose. During following three months four similar attacks accompanied by aura and severe epistaxis. On admission, Aug. 19, 1907, complained of above symptoms and of headache and distress in epigastrium.	Skin very dusky; lips, tongue, gums and conjunctivae blue. Spleen one and a half inches below costal margin. Lungs normal. Heart forcible and accelerated. Dilated veins and venules; marked pulsation of carotids; blood-pressure 120. Skin slightly pigmented. Decayed teeth. Fingers slightly clubbed and nails incurvated. Atrophied uterus. Urine showed slight trace of albumin and occasional traces of indican.	Red cells 5,917,500 to 7,508,000. Hemoglobin 110-112. White cells 4,000 to 6,250. Polys. 64 to 76 per cent.; Lymph. 24 to 31 per cent.; Eosino. 0 to 1 per cent.; Transf. 0 to 4 per cent.	No improvement in hospital. Potassium iodid, oxygen inhalations, and high colonic irrigations all without much benefit. She felt better after withdrawal 7½ ounces venous blood but this procedure discontinued account of weakened condition. Patient discharged Sept. 24, 1907. Most severe symptoms were headache, indefinite abdominal pains, occasional palpitation and malaise. Had one slight convulsion with rather severe epistaxis. Three months after leaving hospital she wrote that she had become quite weak and averaged two fainting spells weekly, followed by severe headache. Also attacks of numbness in left leg and was growing progressively weaker and more cyanosed. Chace calls attention to this patient being the youngest reported (since then Sandesky has reported a patient of the same age—Case 67).
59.— Bar-dachzi	Female, aged 59. Three months ago, after some excitement, noticed twitching in right hand, which soon extended to whole body with the general appearance of chorea.	Cyanosis of face. Spleen enlarged. Liver enlarged.	Red cells 10,900,000. Hemoglobin, Fleischl, 135. White cells 7,000. Later red cells 9,750,000; hemoglobin 120 and white cells 13,000. Color index 0.62.	Under treatment with bromids and sodium iodid, and later sajodin, chorea decreased, patient improved and left hospital.
60.— Miller	Male, aged 39. Began to suffer at Christmas, 1906, from dyspnea, pains in chest and legs and occasional bleeding from gums. No history of syphilis.	Great cyanosis of face, lips, fingers and toes. Spleen enlarged and hard. Heart normally located; impulse powerful; first sound labored and second sound accentuated at aortic area. Blood-pressure 124. Legs swollen. No clubbing. Urine shows trace of albumin.	Red cells 11,300,000. Hemoglobin 180. White cells 15,300. Polys. 81 per cent.; lympho. 12 per cent.; no abnormal cells; coagulation time 6 minutes at 98.6 F. Viscosity 16. Oxygen capacity 1.480 c.c. Blood vol. 4.765 c.c. Color index 0.8.

- 61.—Thompson
Male, aged 57; employed in gas works. Syphilis 38 years ago; employed in gas works during the past three years. Has been gradually becoming blue and complains of headache and weakness. At one time showed signs of mental disturbance.
- 62.—Comesatti
Male, aged 32. Does not use alcohol nor tobacco. Denies venereal disease. About a year ago first had headache and face began to show cyanosis. Six months later vertigo, cyanosis. Spleen much enlarged. Liver just palpable. Arterial, venous and capillary blood-pressure normal.
- Cyanosis of face, lips, etc. Spleen much enlarged. Liver enlarged. Veins of forehead and abdomen distended. Fundus oculi shows marked venous congestion. Temperature about 99.4 F.
- Red cells varied from 10,000,000 to 13,000,000. Hemoglobin 140. Blood pigment normal. Total volume blood $2\frac{1}{2}$ to 3 times the normal. Oxygen capacity $2\frac{1}{2}$ times normal.
- Died of tuberculous. No autopsy.
- 63.—Seufert
Female, aged 61; German; housewife. Mother died of heart disease at 60; one brother of phthisis at 50; two sisters at 60; unknown cause. Usual disease of childhood. Menstruated ages 14 to 41. Never pregnant; no uterine or ovarian disease. After menopause developed cystic goiter which grew up to time of death. Six years ago headache, giddiness and weakness. Five and half years ago swellings both sides of abdomen. Since beginning of this trouble sweating, indigestion without vomiting, and spots over body which are red in warm weather and purple in cold and most numerous on face and limbs; mucous membranes also being purplish blue. Mucous diarrhea for past year.
- Red cells 6,850,000 to 8,500,000. Hemoglobin 95-120. White cells 7,000 to 12,500. Polys. 69-87 per cent.; lymph. 6-12 per cent.; mononuc. 5-15 per cent.; Eosinophils 1-9 per cent. Red cells 15,500,000. Hemoglobin 180. White cells 14,000. Neutrophilic leukocytes 53 per cent. Eosinophilic leukocytes 4 per cent.; Basophilic leukocytes 2.5 per cent.; mononuc. leukoc. 3 per cent.; small lymph. 23 per cent.; large lymph. 14.5 per cent.; coagulation time one minute. Red cells normal in size and shape with an occasional normoblast. Blood very dark and viscid and spread on slide with great difficulty. Color index 0.58.
- Died in March, 1909. Treatment in this and in the following case had little, if any, influence on the course of the disease. Arsenic, quinin and the x-ray were faithfully tried but without any result. Inhalations of oxygen gave temporary relief for at least twenty-four hours at a time. Removal of 250 c.c. of blood in this case gave only transient relief for not over forty-eight hours.

TABLE 1.—(Continued)

Case No. and Author* 64.— Seufert	History	Examination	Blood Examination	Outcome, Treatment, Autopsy and Remarks
	Female, aged 43; Russian Jewess; housewife. Mother died at 51, having been bed ridden each winter for twenty years with cough and hemoptysis. One sister died at 48 of kidney disease. Measles at 6; normal menstruation 14 to 42. Married at 20; five children and four miscarriages. Health perfect up to 17 when began to complain of dizziness and nausea, followed by headache and severe pain in fingers and toes with no relief night or day. Six years ago miscarriage and severe hemorrhage with prompt relief in fingers. Came under observation in 1906 account of weakness, dizziness and inability to stoop account of lump in left side. Intense thirst since the beginning of disease. Sleeps well but cannot lie on left side.	Face, and especially lips, nose and cheeks, purple; conjunctive, tongue and buccal mucosa very purple; purple patches over body, especially arms and legs. Spleen extends to iliac crest. Liver, at first normal, now greatly enlarged and both organs smooth, hard and not tender. Varicose veins, especially of left leg, but no edema. Nails markedly hippocratic. No glandular enlargement. Skin flabby and mused atrophic. Pulse 85 to 95. Reflexes normal. Pupils equal and respond promptly to light; ophthalmoscope shows some tortuosity and enlargement of veins. Uterus prolapsed. Urine shows urea 2.5, uric acid greatly increased and diazo reaction always present; specific gravity 1.020.	Red cells 15,000,000. Hemoglobin 170. White cells 12,500. Neut. leuko. 73 per cent.; Eosin. leuko. 2 per cent.; Baso. leuko. 1.8 per cent.; Mononuc. leuko. 3.2 per cent.; Small lymph. 16 per cent.; Large lymph. 4 per cent. Coagulation time 1 minute. Occasional normoblasts and megaloblasts. Color dark red and coagulated so quickly it was difficult to make blood counts. Color index 0.57.	Splenic enlargement was first noticed by patient after birth of last child nine months previous to time when she came under observation. In the two and a half years during which she was under observation all of her symptoms have become more severe, the general weakness more pronounced, the spleen has varied very little in size and she has lost 50 pounds in weight. As to treatment, see preceding case.
65.— Drummond	Male, aged 44; miner. Admitted to hospital in August, 1908, with a history of headaches and giddiness over a period of ten years.	Lips deep blue; tongue and palate brilliant dark scarlet; legs and hands red. Spleen enlarged. Heart not enlarged. Pulse full. Blood-pressure 120.	Red cells 12,000,000. Hemoglobin 170. White cells 12,000; mostly polymorphonuclears. Color index 0.71.	After a short time in hospital patient returned to work, but symptoms became aggravated with vomiting and occasional blood in urine.

Treatment arsenic and iodids, Results not mentioned.

Cyanosis of face. Spleen greatly enlarged. Temperature normal. Thoracic arteries tortuous. Urine shows trace of albumin; sp. gr. 1.010.

Male, aged 33; soldier. Malaria and typhoid fever in 1904. Complaints of exhaustion after slight physical exertion; also of giddiness and faintness, pain in left hypochondrium and cough.

Red cells 10,600,000. Hemoglobin 120-160. White cells 18,000 to 23,000. Polys. 80-83 per cent.; Lymphocytes 14-18 per cent.; Large mononuc. 0-2 per cent.; Eosin. 0-3 per cent.

Cyanosis. Spleen enlarged. Heart displaced.

Red cells 6,380,000. Hemoglobin 105. White cells 8,700. Polys. about 71 per cent.; Mononuc. about 28 per cent.; Eosinophils 1 per cent.

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Female, aged 17. Complaints of cough, expectoration, etc.

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66.—
Snyder

Marked cyanosis of skin and mucous membranes. Spleen three finger breadths below costal margin. Liver, lungs and heart practically normal. Varicose veins of legs. Blood-pressure 145. Eyes hyperemic. Urine practically normal.

Red cells 8,000,000 to 10,000,000. Hemoglobin 150-240. White cells 6,600 to 8,500. Polys. 75 per cent.; lymph. 16 per cent.; eosin. 5 per cent.; myeloc. 4 per cent. Sp. gr. 1.060 to 1.076. Viscosity 20 to 40.

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Female, aged 48; single. No hereditary taint. Sickly for years. For past four years bluish red discoloration of skin, pain in joints, headache, dizziness, weakness, palpitation, dyspnea and disturbances of digestion.

.....

67.—
Kuttner

Marked dark reddish discoloration of face, upper part of chest and hands. Spleen markedly enlarged.

.....

Dr. H. D. Jump has kindly given permission to mention the case of a man who has been under his observation for some time and who was presented by him before the West Branch of the Philadelphia County Medical Society in April, 1912. Dr. Jump will report this case elsewhere.

.....

69.—
Jump

*For references see text.

TABLE 2 (CLASS B).—CASES WITH CYANOSIS AND SPLENO-MEGALY AND WITH A SYSTOLIC BLOOD-PRESSURE EXCEEDING 150

Case No. and Author*	History	Examination	Blood Examination	Outcome, Treatment, Autopsy and Remarks
70.— Oler	Male, aged 44; physician. Habits good. No previous illness. For five years fulness of head, giddiness, cyanosis, and constipation.	Marked general cyanosis. Moderately enlarged spleen (edge palpable). Liver not enlarged. Lungs normal. Heart slightly enlarged but no mur- murs. Blood-pressure 170 to 200. Conjunctivæ injected. Urine shows trace of albumin and a few hyaline and granular casts.	Red cells 9,952,000. Hemo- globin 120. White cells 4,000. Color index 0.6.	
71.— Weber and Watson	Male, aged 58; Dutchman. Always subject to indigestion, constipation, headache and insomnia. For past six years liable to blueness of nose and extremities. Hematemesis five years ago. Fractured rib three months ago. Signs of insanity de- veloped shortly after and removed to asylum.	Marked cyanosis of face and extrem- ities. Spleen enlarged. Liver nor- mal. Lungs slightly emphysema- tous. Heart normal. Pulse, high ten- sion. Blood-pressure 140 to 170. Urine shows cloud of albumin, ex- cess of urobilin but no casts.	Red cells 9,000,000 to 11,000,- 000. Hemoglobin 170. White cells 7,500 to 12,000. Differ- ential normal. No abnormal red cells. Sp. gr. over 1,066.	Patient died soon after in syncope with increased cyanosis. Autopsy: Spleen 23 ounces, scarred with old infarct; otherwise substance normal. Liver normal. Lungs engorged, mod- erately emphysematous and con- tained few small infarcts. Left ven- tricle hypertrophied; old vegetation aortic valve and slight thickening mitral. Stomach congested and round ulcer near pylorus. Marrow of long bones red, consisting chiefly of normoblasts and myelocytes. Weber considers changes insufficient to account for symptoms.
72.— Parkes Weber	Female, aged 27; Roumanian Jewess. Inflammation of womb and swelling of left extremity seven years ago after birth of second child. For two or three years headache, giddiness and prostration. Two years ago acute erythromelalgia of left foot. Year ago polycythemia and enlarge- ment of spleen.	No marked cyanosis but fingers and toes rather livid and tongue bluish. Spleen extends 1 inch below costal margin. Liver not enlarged. Lungs and heart normal. Cutaneous ves- sels overfilled. High pulse tension. Blood-pressure 160. Vessels of fun- dus oculi engorged and tortuous. Urine about normal.	Red cells 8,000,000 to nearly 11,000,000. Hemoglobin 145- 180. White cells 4,000 to 9,000. Polys. moderately in- creased. Sp. gr. 1,072-1,078. Nucleated reds present. To- tal volume and viscosity greatly increased. Cryos- copy and resistance hemol- ysis about normal.	Condition about the same two years later. Some improvement occurred but polycythemia persisted. Total volume blood 5,600 to 6,000 c.c. (normal individual estimated to possess 4.6 c.c. per 100 gm. of body weight). See text as to blood-vis- cosity.

73.—
Ronald-
son

Female, aged 62. Has had six children, one dying of phthisis and one of heart disease. Has always been of present color. Twenty years ago rheumatic pains confined her to bed for a short time; does not think she had fever. Constipated for three years. Easily tired and dyspnea on exertion for two years. Slight vertigo on stooping.

Red cells 8,152,000 to 9,175,000. Hemoglobin 130-145. Polys. 77 per cent. Lympho. 23 per cent. Blood very dark and viscid. Glycogen reaction distinct but not marked.

Face dusky purple; numerous dilated venules over cheeks and nose; rest of body redder and hands almost rose tint; mucous membranes livid; dilated capillary points over trunk. Spleen 2 inches below costal margin. Liver slightly enlarged. Lungs normal. Heart somewhat enlarged; first sound sometimes reduplicated. Arteries thick and tortuous. Blood-pressure 180 to 190. Urine shows faint trace of albumin and a few hyaline casts; much urobilin and urochrome present.

Male, aged 43. Ague at 12. Pneumonia at 33. Cough and dyspnea for some years. For last six years marked cyanosis face and hands, attacks of headache, giddiness and vomiting and inability to bleeding from gums and nose.

Red cells about 11,000,000. Hemoglobin 180. White cells 11,000. Moderate relative increase of polymorphonuclear eosinophils. Color index 0.81.

Cyanosis of face and extremities. Spleen enlarged. Liver enlarged. Lungs normal. Heart hypertrophied. Blood-pressure 180. Conjunctivæ injected. Veins distended. Urine shows albumin but no casts.

75.—
Saund-
by

Male, age not stated. Two years ago swelling of legs following influenza. At that time was florid with a blue tongue. No enlargement of spleen and no blood-count, case being regarded as thrombosis inferior vena cava. In a week, after rest in bed, swelling of legs disappeared, but they remained painful. Although better, was never able to resume work. A year ago readmitted for return of leg swelling and for swelling of abdomen lately noticed. Some dyspnea.

Red cells 7,144,000 to 9,200,000. Hemoglobin 140-190. Differential normal. Viscosity about twice normal (9.4). No abnormal reds. Sp. gr. 1.075. Coagulation time 8 to 10½ minutes.

Florid. Tongue blue. Spleen palpable. Liver half way to umbilicus. Heart somewhat enlarged. Veins distended. Blood-pressure 170 to 180. Edema walls of chest and abdomen. Legs swollen. Knee-jerks absent. Retinal veins full. Dermatographia present. Urine shows albumin and much indican.

Treatment: Arsenic, iron, digitalis, adrenalin chlorid, quinin, diuretin and bleeding up to twelve ounces with temporary relief. Colon has been systematically irrigated with large amounts (5 to 6 pints) of water, which for some time contained 5 gr. alpha naphthol to the quart; all without appreciable relief. Erythrol tetranitrite tried without much benefit (blood somewhat reduced in pressure). Also tried vinegar (old idea that it thins the blood) with some apparent effect on the polycythemia.

*For references see text.

TABLE 2.—(Continued)

Case No. and Author*	History	Examination	Blood Examination	Outcome, Treatment, Autopsy and Remarks
76.— Senator	Male, aged 58; Russian Pole; merchant. Healthy all his life but for years has had red face. Two years ago weakness, loss of appetite and vertigo; was then markedly cyanotic with enlarged liver and spleen, nephritis and polycythemia. Three months ago severe epistaxis, after which felt better. Two weeks later paralysis of right hand and right lower facial nerve region, as well as aphasic disturbances.	Mucous membranes dark blue; at one time markedly cyanotic. Spleen and liver enlarged. Heart normal. High arterial tension; blood-pressure 155 to 160. Slight paralysis extremities right side. Slight motor aphasia. Urine: 1,400 to 1,700 c.c., sp. gr., 1.014 to 1.017; albumin 0.4 to 0.7.	Two years ago: red cells 8,710,000; white cells 18,480. Last year: red cells 6,950,000; white cells 12,500; hemoglobin 145; color index 1.05. Polys. 86.4 per cent.; Mononuc. 2.3 per cent.; Lymph. 5.8 per cent.; Eosin. 2.9 per cent.; Mast cells 2 per cent.; Myeloc. 0.7 per cent.	Treatment two years ago dietetic and hygienic. Three months ago: injections of sodium cacodylate (0.05 to 0.075 daily); spleen much reduced but blood unaffected. K. I. produced increase of redness and conjunctivitis and was given up. Faradization of spleen, quinin, albumin-poor diet, venesection and leeches all without much effect.
77.— Nicola	Male, aged 51; married; home Oklahoma. Well during early life. Positively denies venereal taint. For three years weekly attacks of headache, face becoming red although extremities cold and clammy. During past six months several severe attacks of headache, requiring hypodermics, and accompanied by giddiness, flashes of light, extreme photophobia, cyanosis of face, neck and finger nails and considerable hemorrhage from gums and pharynx. Feels "groggy" all the time and mind is cloudy. Bowels obstinately constipated. No dyspnea.	Face and neck dark red; hands less so and unexposed surfaces normal color; nose, ears, lips, tongue and mucous membranes all bluish red. Spleen 1 inch below costal margin. Lungs and heart normal. Blood-pressure 153. Conjunctive injected; veins of fundus oculi blue, dilated and tortuous. No blood or parasites in feces. Urine shows considerable indican and uric acid crystals and a few hyaline casts.	Red cells 6,000,000 to 8,000,000. Hemoglobin, Dare, 120. White cells two and a half times normal. Polys. 84.5 per cent.; S. lymph. 6.8 per cent.; Myeloc. 1.6 per cent. Megaloblasts three times in eight counts. Two normoblasts in eight counts. Color index 0.75 to 1.00.	Three attacks in hospital; first severe headache with marked cyanosis and capillary hemorrhage from mouth and pharynx; second pain around heart and down left arm with increased cyanosis; and, third, pain and tenderness in calf of right leg and distressing pruritus after bathing, affecting legs especially. Under symptomatic treatment, tonics and eliminatives, patient improved and cyanosis almost disappeared, but polycythemia not affected by treatment nor by x-ray or K. I.
78.— Parker and Slocum	Male, aged 43; American; laborer. Asthmatic attacks since 30. Six years ago attack of "asthma" with unconsciousness. Four years ago noticed blueness face, hands and feet with variable swelling. Four months ago, blueness, which had disappeared, became marked, especially when working or excited, and palpitation, dyspnea, severe frontal headache, dizziness and prominence of the eyes became marked.	Startling general cyanosis, especially of nose, lips, chin and ears; hands and feet moderately blue; palate and tongue deep purple. Spleen enlarged (see "Remarks"). Liver just palpable. Lungs emphysematous; dyspnea on exertion. Heart negative at first (see "Remarks"). Radials moderately sclerosed; pulse fuller left than right; blood-pressure left 156, right 146. Eyes prominent (see "Remarks"). Conjunctivae suffused. Urine shows moderate albuminuria and many granular casts and cylindroids. X-ray examination: see "Remarks."	Red cells 6,540,000. Hemoglobin 100 plus. White cells 6,500. Polys. 67.6 per cent.; small lymph. 14.8 per cent.; large lymph. 3.8 per cent.; eosinophils 3.8; mast cells 1.6 per cent.; degenerated red cells 8.4 per cent. Later: red cells 7,400,000. Sp. gr. 1.062. Coagulation time less than one minute. See also "Remarks."	Temporary improvement; patient left hospital in 1908. Fluoroscope and radiogram revealed non-pulsating shadow in mediastinum thought to be a tumor. Eyes showed more or less blurring of vision and occasional diplopia; vision 0/D 100; 0/S 20/50. Veins of fundus markedly tortuous and dilated. Retina deeper red than normal and edematous. Two years later: heart enormously dilated, spleen just palpable, lungs emphysematous, red cells 7,200,000, hemoglobin 120, white cells 10,320 and blood-pressure 136.

79.—

Parker
and
Slocum

(cyanosed. Spleen 1 inch below costal margin. Liver not enlarged. Lungs negative. Heart moderately enlarged. Blood-pressure 165. Slight general glandular enlargement. Eyes: vision 0/D 6/7.5; 0/S 6/9; retina hyperemic; veins much engorged, tortuous and dark in color.

Red cells 8,000,000 to 9,000,000. Hemoglobin 110. White cells 14,000. Polys. 87 per cent.; S. lymph. 2.2 per cent.; L. lymph. 3.2 per cent.; Eosin. and mononuc. 1.6 per cent.; myelo. 1.4 per cent.; mast cells 0.8 per cent.; degenerated cells 3.8 per cent. One normoblast and one megaloblast. Some irregularity in red cells.

80.—

Umney

Female, aged 34; married. Family history of nervousness. One brother died from phthisis. As a girl suffered from anemia. Soon after marriage noticed bluish color to complexion, which was greatly intensified in cold weather. General health, however, was good. Meneses irregular since miscarriage in August, 1902. Came under observation in October, 1905, on account of rather profuse menstruation after absence of four months. When seen by Umney this had ceased but she had hematuria lasting a few days and followed by a permanent albuminuria.

Whole body remarkable color; cheeks, nose, lips, ears and fingers bluish red and skin of chest, back and abdomen uniformly red. Palms of hands also quite red. Spleen three or four finger breadths below ribs; not tender. Liver not felt. Lungs and heart normal. Radial arteries considerably thickened; pulse regular and tense. Blood-pressure 170 (see "Remarks"). Tiny venules noticed on cheeks. No clubbing of fingers. Conjunctivæ injected. Kidneys somewhat movable and somewhat enlarged. Urine shows considerable albumin and a few granular casts and red cells.

Male, aged 50. Case presented before the St. Louis Medical Society, showing polycythemia, splenomegaly and marked cyanosis of the face, hands and feet.

81.—

Myer

Red cells 12,880,000. Hemoglobin 120. White cells 20,600. Polys. 92 per cent.; lymph. 3 per cent.; large mono. 2.3 per cent.; eosin. 1.3 per cent.; baso. 1.3 per cent. Coag. time $7\frac{1}{2}$ to 8 minutes. Blood flows slowly, is dark and viscid. Color index 0.46.

Blood from different parts body shows practically same findings. Just below splenic mass is a palpable mass of much the same consistency, apparently separated from the spleen and measuring 11 by 6 cm. and which is either a part of spleen or possibly a supernumerary spleen. Myer suggests that lues be borne in mind as a possible etiologic factor and proposes instituting active antileptic treatment.

82.—

Stache-
lin

Male, aged 50. For 18 years palpitation, tinnitus aurium, pain in thorax, headache and vertigo.

Red cells 5,000,000 to 6,200,000. Hemoglobin 147-167.

83.—

Stache-
lin

Bluish red color. Spleen shows percussion enlargement. Liver not enlarged. Heart slight enlargement to the left. Blood-pressure 185 to 200.

Red cells 6,200,000. Hemoglobin 163. Color index 1.31.

TABLE 3 (CLASS C).—CASES WITH EITHER CYANOSIS OR SPLENO-MEGALY ABSENT AND IN WHICH BLOOD-PRESSURE DOES NOT EXCEED 150

Case No. and Author*	History	Examination	Blood Examination	Outcome, Treatment, Autopsy and Remarks
84.—Moutard-Martin and Lefas	Female, aged 49. Typhoid in childhood. For past year pain and swelling in left hypochondrium.	No cyanosis. Spleen enormously enlarged. Liver slightly enlarged. Lungs, heart and urine normal.	Red cells 8,200,000. White cells 31,400.	Died soon after with vomiting and fetid diarrhea. Autopsy: Spleen 1,750 gm. and showed scattered nodules, apparently tuberculous. Liver 2,000 gm. Lungs and heart normal.
85.—Cabot	Female, aged 46; massense. Six years ago had fit with unconsciousness and thick speech. Four years later mental and muscular weakness, face purple and eyes injected.	Cyanosis of face and tongue. No splenic enlargement reported. Heart normal. Urine showed traces of albumin and a few hyaline casts.	Red cells 10,460,000. Hemoglobin 150. White cells 20,000. Color index 0.7.	Died within a few months of middle meningeal hemorrhage. Autopsy: revealed nothing in addition except great congestion of all the viscera.
86.—Hall	Female, aged 61; Jewess; born in Germany. Dyspnea and palpitation since menopause. Sleeps well; appetite good. No pain; always thirsty. Mother of six children. Patient's son thinks that patient's mother presented a similar discoloration of the lips and face and enlarged veins during latter part of her life. The patient's children are still under middle age and none has shown any symptom of this condition.	Startling cyanosis; lips and tongue of the color of a ripe Concord grape; slightly less marked on hands and still less on trunk and lower extremities. Spleen and liver negative. Lungs slightly edematous; marked dyspnea on slight exertion. Heart slightly enlarged. Arteries moderately atheromatous; veins distended and tortuous; pulse of increased tension. Lips tremulous. Eyes: see "Remarks." Urine contains albumin and casts; sp. gr. 1.012.	Red cells 10,000,000. Hemoglobin 170-200. White cells 6,500.	Patient continued in same state of health and without marked alteration in vision from June, 1903, to June, 1904, when she died after a few hours illness with symptoms of acute cardiac failure. No autopsy. Jackson (in Ophthalmology, Milwaukee, 1907) shows two plates of the eye-grounds in this case and goes fully into the eye condition over a period of three years. The vision steadily decreased; there was low myopia with slight rotary nystagmus and epiphora. Pupils became unequal and light reaction was disturbed. There was great dilatation of left central retinal vein where it disappeared in nerve head. Jackson says: "In June, 1903, the sinus of left nerve is probably twice as large as a year ago and differs from anything I have seen before."

87—

Collins

Male, aged 42; Hebrew; peddler. After being under observation for four years on account of progressive muscular atrophy, patient developed cyanosis of extremities.

Male, aged 35. Typhoid ten years ago. For two years headache, constipation and pain in right hypochondrium. A year ago liver found to be enlarged.

88—

Turk

Cyanosis of extremities. Spleen not enlarged. Liver not enlarged. Lungs, heart and urine normal.

Red cells 8,400,000.

Hemoglobin over 100. White cells normal.

Red cells 8,000,000, falling to 5,160,000 before death. White cells 10,000. A very few nucleated reds, erythroblasts and myelocytes.

Patient became more jaundiced and died soon after with hemorrhage from nose, stomach and intestine. Autopsy: Spleen firm, weighing 930 gm., and bound by adhesions to liver. Hypertrophy and cirrhosis of liver with regenerative changes (multiple adenomata). Had been diffuse hemorrhage from mucous membrane of duodenum. Marrow of long bones dark red and of fairly firm consistence.

89—

Kikuchi

Female, aged 47.

Cyanosis present. Spleen not enlarged. Liver not enlarged. Lungs emphysematous; chronic bronchial catarrh with bronchiectasis. Heart rapid and arrhythmic. Patient dyspneic. Abdominal wall edematous. Urine shows trace of albumin, urobilin and indican.

Red cells 5,700,000 to 6,215,000. Hemoglobin 154-168. White cells 7,500 to 9,400. Numerous normoblasts present in stained specimen.

Patient died on the second day. Autopsy: Liver and spleen small and firm and spleen contains much blood. Lungs: emphysema, chronic bronchial catarrh and bronchiectasis. Dilatation right heart. Numerous hemorrhagic erosions of stomach and duodenum. Ulcer left leg. Universal mechanical hyperemia. Bilateral hydrothorax. Edema lower extremities. Old tuberculous. Chronic arthritis deformans.

Male, aged 36. Has suffered for a year or two from headache, giddiness and dyspepsia. A year ago hematemesis and melena; the liver slightly enlarged but the spleen normal. Two months ago spleen and liver greatly enlarged.

No cyanosis but mucous membranes of mouth very red. Spleen reached to iliac crest. Liver enormous. Lungs normal. Heart: apex beat displaced upwards to the fourth interspace. Urine shows albumin, casts, urobilin and excess of indican.

Red cells 10,107,000. Hemoglobin 185. White cells 34,000. Polys. rel. increased. Lymph. 4 per cent.; large mononuc. 4.8 per cent.; eosin. 6.8 per cent.; mast cells 1.4 per cent. One myelocyte and one normoblast. Blood dark and viscid. Color index 0.91.

Later the red cells from ear were 10,426,000 and at same time from finger were 9,700,000.

*For references see text.

TABLE 3.—(Continued)

Case No. and Author.	History	Examination	Blood Examination	Outcome, Treatment, Autopsy and Remarks
91.— Zaudy	Female, aged 27; single. Gastric fever eight years ago. At about same time the spleen enlarged. Menorrhagia until two years ago. Severe dyspnea for some weeks.	No cyanosis but very bright red complexion. Spleen reaches to umbilicus. Liver not enlarged. Lungs, heart and urine normal.	Red cells 9,400,000. Hemoglobin over 100 (limit of seatle). White cells 18,000. No abnormal red cells.	Dyspnea soon disappeared and she ceased to remain under observation.
92.— Wein- traud	Male, aged 36. Malaria at 19. Always asthmatic but better since operation on nose at 26. Two years ago well marked cyanosis of face and extremities, spleen, liver and heart enlarged, lungs somewhat emphysematous and urine showed albumin. Fifteen months ago phlebitis of left leg. One year ago spleen and liver no longer palpable.	Face purple. Spleen no longer palpable. Liver $2\frac{1}{2}$ inches below costal margin. No dyspnea. Blood-pressure 110. Conjunctivae injected. Urine shows albumin but no casts.	A year ago red cells were over 10,000,000. At present red cells 7,368,000; hemoglobin 170; white cells 9,800. Sp. gr. 1.066. Color index 1.16.	
93.— Axel Blad	Female, aged 34. Pain in epigastrium and left hypochondrium.	Face congested. Spleen enlarged.	Red cells 11,000,000.	Spleen excised and death occurred a few days later. Autopsy: Showed death to be due to profuse internal hemorrhage. Spleen showed some small infarcts and microscopically seemed to show enlargement to be due to simple hyperplasia. Liver slightly enlarged and microscopically showed early cirrhotic changes. Condition of bone marrow not stated.
94.— Reiss- mann	Female, aged 18. For four years lips blue and skin dusky. Three years ago had attacks of unconsciousness and vomiting, complained of frequent headaches and eyes became prominent. Regular menstruation up to five months ago when she developed amenorrhea. Two years ago diarrhea and vomiting.	Slightly dusky, dry skin; lips blue; mouth and fauces very red. Spleen not enlarged. Liver dulness slightly increased upwards. Breathes a little hurriedly but lungs healthy. Heart normal; venous pulsation in neck; pulse 160. Eyes distinctly prominent; Von Graefe's sign absent; fine tremor of hands; thyroid not enlarged. Optic disks red and somewhat engorged. Temperature 100. Some tenderness right lumbar and subcostal regions. Urine shows trace of albumin, much chromogen and decided acetic acid and trace of acetone.	Two years ago; red cells 7,404,000. Hemoglobin 124. White cells 5,600. Blood very rich color. Coag. time 30 seconds. Viscosity much increased. Color index 0.97. After hemoptysis: red cells 5,776,000; white cells 12,000. Following March: red cells had fallen to 4,736,000; white cells 7,000.	Vomiting and diarrhea ceased a few days after first observation but general condition gradually became worse. Continuous pyrexia for over a month. Operation for liver abscess but no pus. After operation patient very ill with dulness both lungs and finally coughed up six ounces bright red blood with improvement. Then signs venous obstruction left leg, persisting for a month. In following March patient well and strong but with slight cyanosis, pronounced on exertion. At present (two years after severe illness) condition much the same. Still slight cyanosis; pronounced on exertion. No excess of red cells but blood more viscid than normal. Note apparent recovery.

95.—Geisbock	Male, aged 39.	Blood-pressure 150.	Red cells 6,475,000. Hemoglobin 124. Color index 0.97.
96.—Geisbock	Male, aged 50.	Heart enlarged and irregular. Blood-pressure 130 to 140. Urine shows albumin and a few casts.	Red cells 7,600,000. Hemoglobin 150. Color index 0.99.
97.—Geisbock	Male, aged 58.	Heart slightly enlarged. Blood-pressure 150.	Red cells 6,565,000.
98.—Levi	Male, aged 56. Denies venereal disease. For 25 years slight cough, which followed a bronchitis. Ten years ago first noticed blueness face, which gradually increased. Late attacks of nausea, vomiting and unconsciousness.	Cyanosis of face, neck, hands, etc. Spleen described as "very firm," but no mention of enlargement. Liver enlarged. Mucous membranes and conjunctivæ injected. Patient "a strong man." Urine shows some albumin.	Red cells 10,740,000. Hemoglobin gr. 29 per cent (Fleischl). White cells 12,200.	Treatment by arsenic and Roentgen rays. Patient left somewhat improved.
99.—Russell	Female, aged 21; domestic. Four years ago complained of dyspnea on exertion. For past year legs swollen at intervals and dusky and swollen appearance of face and eyelids. Has had occasional attacks of precordial pain and fits after exercise in which has lost consciousness and has occasionally passed urine. Blood a year ago showed a large excess of red cells.	Face dusky red and swollen; hands and feet dark red; mucous membranes, except lips, not cyanosed; numerous scattered pigment spots over body. Spleen not palpable but dullness increased. Lungs normal. Heart somewhat enlarged; short systolic murmur at apex; pulsation and shock second interspace; pulse 120, small and low tension; with rest soon fell to about 80; blood-pressure 115. Slight clubbing of fingers. Eyes: see "Remarks." Urine shows: 0.1 per cent. albumin, 1.3 per cent. urea and a few hyaline and granular casts.	Red cells 6,297,000 to 8,650,000. Hemoglobin over 120 (limit of scale). White cells 5,600 to 7,000. Polys. 61.4 to 74 per cent.; lymph. 19.3 to 29 per cent; large mono. and trans. 6.3 to 7.9 per cent.; cosino. 0.2 to 1.9 per cent. No nucleated reds nor abnormal sized or shaped red cells. A very few myelocytes.	Acute symptoms improved with rest in bed but polycythemia did not disappear. Eyes: conjunctivæ slightly edematous with large and tortuous vessels. Optic disks: considerable blurring of edges, obviously due to edema; right disk veins very much enlarged and tortuous; arteries also large. Outer part of disk showed remarkable group small arterioles; enlarged vessels scattered about retina. Near macula small patch of pigment, "the result of former chorioiditis." Left disk similar in lesser degree.
100.—Dence	Female, aged 42. Cyanosis face and extremities for two years. Also shooting pains in hands and liability to bleeding from gums.	Well marked cyanosis of face and extremities. Spleen not mentioned. Liver slightly enlarged. Lungs and heart normal. Conjunctivæ injected. Urine normal.	Red cells 8,350,000. Hemoglobin greatly increased. White cells 8,400.

* For references see text.

TABLE 3.—(Continued)

Case No. and Author*	History	Examination	Blood Examination	Outcome, Treatment, Autopsy and Remarks
101.— Pfeiffer and Behr	Male, aged 37; machinist. Denies venereal infection. Drinks moderately. Great exertion in military maneuver. "Beating in body sensation." From his thirty-fourth year severe nocturnal headaches and cyanosis of face which has gradually increased. Later pain under right costal arch, dyspnea and cyanosis of whole body, especially upper half. No diagnosis except catarrh, bronchitis and albuminuria.	Patient "a strong man." Cyanosis of body, more marked in upper half. Veins of skin very distinct. Spleen apparently not enlarged. Liver enlarged. Heart normal. Conjunctive injected; moderate choked disk both sides; vision 8/8; retinal veins dilated and tortuous. Urine shows albumin and urobilin but no casts. Blood-pressure slightly increased.	Red cells, on nine counts, from April, 1905, to February, 1906, varied from 6,605,000 to 9,100,000. Hemoglobin 110-145. White cells 6,360 to 15,400.	Treatment, "as usual without success." Patient died of cardiac insufficiency after being under observation for five years. Autopsy: Aortic insufficiency; endocarditis; aortic valves; some endarteritis. Liver indurated from stasis. Hyperemia throughout alimentary tract. Small hemorrhage in kidney. Hyperemia of testicles; brain softened. Eyes: Behr (Kin. monats. f. Augenh., 1911, xlii, 672) goes very fully into eye findings and says this is the first case showing choked disk.
102.— Mc Quitty	Female, aged 68. Family tendency to arterial degeneration. Ten years ago typhoid. Two years later slight congestion of the liver. Then healthy up to two years ago when had diarrhea followed by severe pain in upper abdomen, skin slight yellow, unusual resistance in gall-bladder region, spleen enlarged and urine normal. In a fortnight better but weak. Continued to have occasional attacks of diarrhea and lost 35 pounds. Complains of weakness and loss of weight.	Cheeks red; tongue very red; sclerotics slightly yellow. Spleen three fingers breadths below costal margin. Liver finger breadth below costal margin. Lungs negative. Apex somewhat displaced to left but no murmurs. Thyroid slightly enlarged. Slight trace of albumin.	Red cells 9,500,000. Hemoglobin 116. White cells 13,000. Polys. 46 per cent. S. lymph. 22 per cent. L. lymph. 27 per cent. Trans. 5 per cent. No nucleated reds. Viscosity increased. Color index 0.61.	In the following January patient began to suffer from giddiness and in March was seized with pain in left side of chest with rise of temperature. She soon developed crepitation and delirium and died on the fourth day. McQuitty calls attention to the absence of cyanosis, marked loss of flesh and strength, decrease in polymorphonuclear cells and increase in large lymphocytes and low color index.

103.— Tooth	Female, aged 52; married. Flushed for years. Three years ago shivering and enlargement of spleen. Several attacks during next three years and six weeks in bed, followed by thrombosis of vein left leg. Leg still swells when she stands. In June, 1906, began to have pain in right foot, followed by gangrene of little and third toes.	Face flushed. Spleen extends below umbilicus. Liver enlarged and tender. First heart sound reduplicated.	Red cells 7,500,000. Hemoglobin 110. White cells 6,500. Color index 0.73.	Patient improved somewhat under mild doses of arsenic. She said that on exertion her skin took on a dark blue color, although no marked cyanosis is seen at present.
104.— Pethy- bridge	Male, aged 67; laborer. For seven months had pain in left side, followed by the appearance of a swelling. He has lost weight and complains of weakness.	Florid but not cyanosed. Spleen to umbilicus in mid-line; not tender. Liver 3 inches below costal margin. No dyspnea. Heart sounds clear; pulse regular, 78; blood-pressure 140. Marked psoriasis, no edema. Retinal veins full but not tortuous; optic disk normal; opacities in lens. Knee-jerk normal. Urine normal.	Red cells 8,320,000. Hemoglobin 140. White cells 12,000. Differential normal. Blood dark and coagulates slowly. Color index 0.84.	Patient is able to be up and about and has no urgent symptoms.
105.— Ambard and Fies- singer	Female, beyond middle life. Had been cyanosed and dyspneic as a child as if had congenital heart disease. General condition improved on commencement of menstruation, but at menopause again became cyanosed and dyspneic.	Plethoric and very cyanosed. Spleen not enlarged. Heart somewhat hypertrophied. Retinal veins tortuous and engorged with blood.	Red cells on first count 7,800,000; on second count (one month before death) 5,615,000.	Dropsy and death. Autopsy: Spleen not enlarged and to naked eye substance appeared normal. Liver engorged but did not resemble nutmeg liver macroscopically or microscopically. Hypertrophy left ventricle; slight thickening aortic cusps. Chronic interstitial nephritis. Bone marrow not examined.
106.— Herring- ham	Female, aged 38. Six years ago was pale and anemic. Later high colored with blue nose and subject to attacks of dyspnea and lividity. Extreme constipation.	Complexion florid, fingers purple. Neither spleen nor liver palpable. Lungs and heart apparently normal. Dyspnea without apparent cause.	Red cells 7,630,000. Hemoglobin 120. White cells 8,800. Polys. 64 per cent. Lymph. 25 per cent. Hyaline 8 per cent. Eosin. 2 per cent. Basoph. 1 per cent. No methemoglobin. No sulphhemoglobin. Color index 0.78.	Soon after examination patient died in one of her attacks of cyanosis and dyspnea. Autopsy: Spleen not enlarged and seemed normal on section. Liver congested but not enlarged. Lungs emphysematous but not of large type. No cardiac disease. Bone marrow not examined. Herringham not satisfied that this was case of erythremia but could not explain it otherwise.

TABLE 3.—(Continued)

Case No. and Author*	History	Examination	Blood Examination	Outcome, Treatment, Autopsy and Remarks
107.— Low and Popper	Admitted into hospital with right hemiplegia of fourteen days' duration.	Spleen much enlarged.	Red cells 9,300,000. Hemoglobin above normal. White cells 23,000.	Death five days after admission. Autopsy: Spleen engorged; increased reticular tissue; pulp chiefly red blood corpuscles and leukocytes; only remnants Malpighian corpuscles. Thrombosis left common carotid and artery left Sylvian fossa with softening left cerebral hemisphere. Chronic interstitial nephritis. Bone marrow dark red; full of dilated blood-vessels; only a few fat vesicles; numerous neutrophilic eosinophils, myelocytes, neutrophilic and eosinophilic polymorphonuclears; fewer small and large lymphocytes and erythroblasts (medium quantity).
108.— Ham	Female, aged 18. Well until 13; then bodily development retarded. Menstruated twice when fifteen but never since. During past two years occasional abdominal pains of uncertain nature. Syphilis taint suspected.	No cyanosis. Spleen three fingers breadth below costal margin. Liver not enlarged.	Red cells 6,000,000 to 7,000,000. Hemoglobin 110. Color index 0.78 to 0.91.	In August, 1908, Dr. Ham informed Dr. Weber that since January (when Weber studied case), under treatment with K. I., iodid of iron and occasionally tincture of perchlorid of iron, patient's general condition distinctly improved but splenic enlargement unaltered and polycythemia slightly increased (compare with Case 35).
109.— Lommel	Male, aged 47; workman. Pneumonia at 14. In 1903 severe pain and commencing gangrene in right foot with absence of pulsation in right anterior tibial artery. Pirigoff's operation performed. In 1906 polycythemia and cyanosis.	Cyanosed. Spleen not enlarged. Heart normal. Blood-pressure normal. Veins dilated. Arteries rigid. Fingers clubbed. Patient thin.	Red cells 9,700,000. Hemoglobin 150. Later red cells 10,200,000; white cells 5,300. Poly. neutrophils 71.8 per cent.; lymph. 19.3 per cent.; trans. 3.7 per cent.; eosin. 0.6 per cent. (Color index 0.78.	No other data.

110.—

Male, aged 44. Total abstainer. No syphilitic history. Began in April, 1906, to suffer from dyspnea, palpitation and giddiness and later from severe headache and epistaxis. These symptoms aggravated by cold.

Very general cyanosis. Spleen and liver not palpably enlarged. Heart's impulse powerful; first and second sounds heard over whole cardiac area; systolic murmur constant at pulmonic area, inconstant at apex. Great clubbing of fingers and toes. Temperature usually subnormal. Slight edema of legs at times. Urine contained a trace of albumin on one occasion.

Red cells 12,010,000. Hemoglobin 140. White cells 10,000. Blood volume ten and three quarter liters. Oxygen capacity 3,375 c.c. Coag. time two minutes at 97.6 deg. F. Sp. gr. 1.062. Viscosity 10.43. Color index 0.58.

Patient improved under treatment in hospital with rest, warmth, venesection, saline infusions, iodids and arsenic.

111.—

Male, aged 52; miner. Father died of bronchitis; mother of heart disease; one sister of phthisis in early adult life. Patient very moderate in use of alcohol and tobacco. Attack of right sided pleurisy at 35 and another at 46. No hectic or malarial history. Present illness began in Nov., 1903, with swelling and pain in abdomen, vomiting, eructations, dizziness, weakness and loss of weight. Florid complexion for three years.

Florid but not cyanosed. Spleen reached to umbilicus. Liver and heart slightly enlarged. Vessels moderately thickened. Blood-pressure 130.

In November, 1905, red cells 4,590,000. Hemoglobin 87. White cells 10,300. Polys. 69.5 per cent.; lymph. 22.5 per cent.; large mono. 4 per cent.; eosin. 4 per cent. Color index 0.94. In 1908 red cells 8,870,000 to 10,870,000. Hemoglobin 106 to 110. Later red cells went as high as 13,250,000. Hemoglobin 120-130. Color index 0.47.

Simultaneous counts from dorsal artery and vein of foot showed, respectively, 11,276,000 and 10,970,000 red cells. During patient's stay in hospital in 1908 tibia explored and bone marrow removed which showed almost complete absence of fat cells, large numbers of nucleated red cells and several myelocytes. General condition temporarily improved on number occasion by *x-ray* only to return to previous condition and without permanent effect on blood or spleen. Patient now in excellent health despite polycthemia and enlarged spleen.

112.—

Male, aged 55. Admitted to Royal Infirmary under Dr. Gibson Feb. 27, 1909, complaining of giddiness, pain in head (especially right side), and vomiting. Family history unimportant; no venereal history. Always healthy except typhoid fever in youth. Four months ago attacks of giddiness lasting thirty seconds and accompanied by severe pain right frontal region and dimness of vision in right eye. Also vomiting without reference to food.

Complexion florid but hardly cyanosed; lips and tongue highly colored. Neither spleen nor liver enlarged. Lungs normal. Heart slightly enlarged; blood-vessels thickened and tortuous. Blood-pressure 130. Conjunctivæ injected and superficial venules much engorged and dilated; fundus oculi darker than normal and vessels greatly engorged with very dark blood. No trace of optic neuritis. Urine shows trace of albumin.

Red cells on nine counts varied from 7,950,000 to 9,100,000. Hemoglobin 100-110. White cells 9,200 to 15,500. Polys. 75-88 per cent. Lymph. 7-17 per cent. Large mono. 2-6 per cent. Eosin. 2-6 per cent. Mast cells 1-4 per cent. Great increase in viscosity.

Thirst, vomiting and constipation greatly alleviated by diet and drug treatment. No other treatment of value. K. I. useless and arsenic aggravated symptoms. Lactogenized milk (1½ pints daily) only helped to bring about a healthy condition of intestinal tract. Patient left hospital with subjective symptoms entirely arrested and at present is in excellent health, but polycthemia still persists.

*For references see text.

TABLE 3.—(Continued)

Case No. and Author*	History	Examination	Blood Examination	Outcome, Treatment, Autopsy and Remarks
113.— Mileh- ner	Male. Case of polycythemia with splenomegaly shown by Dr. Milehner before the Berlin Medical Society. The patient sought advice on account of dyspnea and pain in left hypochondrium.	Remarkably red face. Spleen enlarged. Urine contained eight times the normal amount of iron.	Polycythemia present but number of red cells not stated.	Venesection proved useless, red cells increasing again after a few hours. X-ray to spleen unsuccessful. Diet containing as little ferruginous material as possible benefited patient's general condition. Milehner states that, of 7,000 patients examined in out-patient department Royal Medical Clinic three were cases of erythremia.
114.— Manges	Female, aged 26. Symptoms began acutely three or four months ago with vomiting. Three weeks later swelling of left side and ascites, and because of this and increased weakness she entered hospital. Was never cyanosed.	No cyanosis. Spleen reached to umbilicus; was hard and with a number of large nodules on its surface. Liver enlarged, hard and with irregular border. Considerable ascites and slight jaundice. Heart: Slight systolic murmur and moderate enlargement of both ventricles. Low grade fever constantly present. Wassermann negative.	Red cells 6,500,000 to 8,000,000. Hemoglobin 120. White cells 35,000.	Clinical diagnosis favored Hanot's hypertrophic cirrhosis but such a diagnosis untenable on account of blood picture. Final diagnosis was an unusual form of polycythemia in which jaundice, ascites, fever, absence of cyanosis and an unusually rapid course were the unusual features. Possible association of hypertrophic cirrhosis and thrombosis of splenic veins occurring during course of polycythemia also referred to.
115.— Horder	Male, aged 51. Healthy until five years ago when enlargement of spleen began to cause discomfort. A year later signs of polycythemia became pronounced.	Spleen enlarged.	Red cells 10,700,000. Hemoglobin 130. Color index 0.61. Later, nine days after venesection for fifth time, red cells 9,500,000.	Horder regards disease as morbid entity involving composition and distribution of blood. Venesection, large amounts being withdrawn, gave constant although transient relief, red cells falling three or four million and other disturbances becoming attenuated after each blood letting. It was repeated six times in two months, from 150 to 700 c.c. of blood being withdrawn.

116.—
Gold-
stein

In 1900 nose began to get red. Then began to have headache. In 1903 trouble with speech.

Cyanosis of arms, hands, lips, nose and face. Spleen and liver not enlarged clinically; spleen found to be enlarged at autopsy. Veins swollen. Tongue trembles. Temperature 98.6. Urine shows some albumin; Sp. gr. 1.040. Left pupil smaller than right.

Red cells 8,000,000. Hemoglobin 150. White cells 17,000. Polys. 90 per cent. Lymph. 8 per cent. Eosino. 1 per cent. Mononuc. 3 per cent. Color index 0.94.

Autopsy: Spleen enlarged. Liver not enlarged. All viscera markedly hyperemic. Brain: much liquid escaped, veins filled, cysts and cicatrices in brain substance give typical picture of softening of brain.

117.—
Dinkler

Male, aged 49. In September, 1909, taken sick with gastro-intestinal trouble and increasing pain in stomach, pressure in head, vertigo, sweating and loss of flesh.

No cyanosis reported. Spleen and liver much enlarged and tender. Blood-vessels very full. Enormous tumor-like thickening of left renal capsule and of wall of bladder. Urine negative.

Red cells 9,937,000. Hemoglobin 144. White cells 13,950. Color index 0.73.

Dinkler states that case will be reported in full elsewhere.

118.—
Sandesky

Male, aged 55. At 34 years of age had acute febrile trouble with cough and dyspnea following overwork. Later cyanosis of face and increased cough.

Red cells 7,414,000. Hemoglobin 120. White cells 14,000. Polys. 72.4 per cent. (neutrophils 63 per cent.). Lymph. 21 per cent. Mononuc. 5.94 per cent. Color index 0.81.

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119.—White

Male, aged 42; Englishman; resident of Australia. Well until three years ago when he began to suffer from indigestion and face took on a deep color. Indigestion has gradually increased, patient has been frequently sick and has undoubtedly vomited blood. He is also liable to marked bleeding from gums and has lost a stone (14 pounds) in weight.

Whole body full-blooded and livid, especially face; tongue clean but livid. Spleen reached umbilicus. Liver just palpable. Lungs and heart normal. Dilated veins various parts of body. Gums bleeding. Eyes blood-shot; slight conjunctivitis; veins overfilled with dark blood. Blood-pressure 130. Urine shows a trace of albumin, a few hyaline and finely granular casts and a few red cells and leukocytes.

Red cells (in Melbourne) 10,700,000. Later (in England) red cells 9,800,000. Hemoglobin 131. White cells 15,300. Polys. 84 per cent. S. lymph. 7 per cent. L. lymph. 7 per cent. Eosino. 2 per cent. Sp. gr. 1.076. No poikilocytosis, polychromatosis, nucleated reds or other abnormal cells. Total volume blood about three times normal for man of his weight. Color index 0.67.

White says: "Judging from the appearance of the fundus oculi, I should say that it would always be easy to recognize. It is remarkable, in view of the enormous volume of blood, that the arteries, heart and blood-pressure were normal. The patient had six times the normal number of red cells and four times the normal percentage of hemoglobin. Such blood must have nearly reached a volume density which would render circulation very difficult."

*For references see text.

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TABLE 3.—(Continued)

Case No. and Author*	History	Examination	Blood Examination	Outcome, Treatment, Autopsy and Remarks
120.— White	Female, aged 57; single. Had in the past suffered from neuritis and erythema and had lost 28 pounds in weight in a comparatively short time. Suffered from severe irregular abdominal pain and some flushing of hands. A large tumor proved on exploration to be an enlarged spleen.	No cyanosis; patient a trifle drawn and pale. Spleen reached $4\frac{1}{2}$ inches below costal margin and an accessory spleen was present. Some dilatation of blood-vessels.	A few days after the operation red cells were 7,375,000; hemoglobin 90 per cent; color index 0.62 and white cells 43,400. Three and one-half months after operation red cells 9,546,000; hemoglobin 117 and white cells 46,350. Color index 0.61.	Operation on August 27, 1911, disclosed a moderately enlarged spleen. Close to the anterior margin was an accessory spleen somewhat larger than a fifty shilling piece. For seventy-two hours after the operation there was an exceptional oozing of blood.
121.— White	Female, aged 28. Healthy until three years ago when began to have pain and discomfort in left hypochondrium sufficient to prevent her doing housework. Eighteen months ago abdomen opened and tumor found to be enlarged spleen.	Nothing abnormal in appearance, and examination revealed only that spleen reached to 2 inches below umbilicus and forward to within an inch of the umbilicus. Blood-pressure 134. Optic disks normal.	Red cells 8,600,000. Hemoglobin 100. White cells 7,000. Polys. 62 per cent. Lymph. 24 per cent. S. lymph. 12 per cent. Eosin. 2 per cent. Color index 0.58.
122.— Kuttner	Face red. Spleen finger's breadth below costal margin. Blood-pressure 140.	Red cells 5,000,000 to 6,000,000. Hemoglobin 85. White cells 13,500. Polys. 64 per cent. Lymph. 35 per cent. Eosin. 1 per cent.
123.— Staehelin	Male, aged 35. For one and a half years congestion of the head, and sense of oppression of heart after exercise.	Reddish color. Spleen showed percussion enlargement. Liver not enlarged. Heart not enlarged. Blood-pressure 140.	Red cells 5,170,000. Hemoglobin 102. Color index 1.57.

Male, aged 52; Russian Jew; grocer. Measles in childhood. Pleurisy at age of 20. In 1906 prostatic abscess with uneventful recovery. Later headache, vertigo, hazy vision and fulness in head. General health fairly good until May, 1910, when began to have attacks of right sided headache with dizziness and shortness of breath. Following these attacks hands, face, lips and nose became dusky, duskiuess lasting two to twenty-four hours. In Autumn, 1910, frequent attacks of indigestion preceding attacks of cyanosis and headache. Since January, 1911, markedly impaired vision, dizziness and lump in throat on swallowing. Has been of reddish color since his youth but only cyanosed for two years.

Male, aged 43; Russian Jew; vest maker. For four years in the army; then for twenty years a vest maker in the United States. Asthma and cough for 15 years. Headache for six years. Hemorrhoids fifteen years; operation for same ten months ago. Somewhat near sighted. Three months ago slight hemoptysis. Two weeks ago began to have severe headache, dizziness and nervousness. Two days ago his wife noticed that his color had changed.

* For references see text.

Face and especially nose, lips, cheeks and ears bluish-red; hands, wrists and arms to elbow bluish-red; pharynx purplish-red; tongue and soles of feet red. Spleen not palpable although it has been just barely so at times during an exacerbation. Lungs slightly emphysematous. Heart normal. Blood-pressure 120. Fingers clubbed with slightly curved nails. X-ray shows many enlarged mediastinal glands. Eyes at first showed double optic neuritis; later choked disk. Urine shows trace of albumin and a few urates, epithelial cells and leukocytes. Hemorrhoids present.

Red cells 5,200,000 to 8,660,000. Hemoglobin 96-140. White cells 6,800 to 10,200. Polys. 54-74 per cent.; Lymph. 15-27 per cent.; Hyaline 7-15 per cent.; Eosin. 2-9 per cent. Myelocytes on one occasion 6 per cent. No nucleated reds. Viscosity markedly increased. Blood very dark.

Cyanosis has changed very little since he was first observed by Lucas in May, 1911. On a number of occasions venesection has been performed, sixteen ounces of blood being withdrawn as a rule, with some temporary improvement in his general condition but without any marked effect on cyanosis and without any permanent improvement in the blood count. Patient states that he has bleeding from the bowel at intervals of six weeks or more with temporary relief.

Red cells 8,430,000. Hemoglobin over 120. White cells 8,800.

See text for treatment. Six months after patient was first seen his condition was unchanged. He had several exacerbations during this time. Twice the symptoms were sufficiently severe to require venesection, which gave prompt but temporary relief. Eye examination revealed only a marked congestion of the conjunctiva and retina.

Face and especially lips and ears somewhat dusky. Whole face markedly so when lies down. Hands slightly cyanosed. Tongue very red and buccal mucosa and pharynx bluish-red. Temperature 99.4 on admission and 98.4 the following day. Pulse 118 on admission and 96 following day. Respiration 32. Blood-pressure 132. Spleen not enlarged. Liver not enlarged. Lungs and heart apparently normal. Eyes: See "Remarks."

TABLE 4 (CLASS D).—CASES WITH EITHER CYANOSIS OR SPLENOMEGALY ABSENT AND WITH A SYSTOLIC BLOOD-PRESSURE EXCEEDING 150

Case No. and Author.*	History	Examination	Blood Examination	Outcome, Treatment, Autopsy and Remarks
126.— Geisbock	Male, aged 55; bank director. Patient overworked and very excitable. Rush of blood to head at times.	Slight enlargement of the heart. A little irregularity of cardiac action. Blood-pressure 170.	Red cells 6,100,000. Hemoglobin 108. Color index 0.89.	Improved after use of iodothylin, the blood-pressure falling to 120.
127.— Geisbock	Male, aged 64. Hard work and some indulgence in alcoholic liquor. Gangrene of right foot with amputation.	Arteriosclerotic gangrene of foot. Blood-pressure 150 to 160. Urine shows a trace of albumin.	Red cells 10,400,000 to 11,320,000. Hemoglobin 156.	Dorsalis pedis artery of the amputated foot was extremely sclerotic.
128.— Geisbock	Male, aged 62; conductor. Right sided hemiplegia.	Cyanosed. Heart enlarged. Blood-pressure 210. Urine shows a trace of albumin.	Red cells 7,100,000 to 8,000,000. Hemoglobin 112.	
129.— Geisbock	Male, aged 60. Patient excitable.	Arteriosclerosis. Hemorrhagic glaucoma. Blood-pressure 190.	Red cells 6,930,000.	
130.— Geisbock	Male, aged 53; factory manager. Patient overworked and subject to apoplectic seizures with disturbance of speech.	Heart enlarged. Contracted kidney. Blood pressure 250.	Red cells 6,840,000. Hemoglobin 120. Color index 0.89.	
131.— Geisbock	Male, aged 49; architect. Overworked and subject to apoplectic attacks.	Heart enlarged. Blood-pressure 200. Urine shows trace of albumin.	Red cells 8,170,000. Hemoglobin 128. Color index 0.78.	
132.— Geisbock	Male, aged 59; civil officer. History of lues and sexual excess. Right hemiplegia.	Blood-pressure 170 to 220.	Red cells 6,030,000; hemoglobin 104. Color index 0.86.	
133.— Geisbock	Male, aged 56; commissioner. History of asthma.	Blood-pressure 180.	Red cells 6,000,000.	
134.— Geisbock	Male, aged 56; factory manager.	Heart enlarged. Blood-pressure 170. Polyuria and albuminuria.	Red cells 6,165,000. Hemoglobin 120. Color index 0.97.	
135.— Geisbock	Male, aged 45.	Heart enlarged. Contracted kidney. Blood-pressure 235. Urine shows albumin.	Red cells 7,030,000.	
136.— Geisbock	Female, aged 52.	Heart enlarged. Blood-pressure 180. Trace of albumin in urine.	Red cells 6,000,000.	
137.— Geisbock	Female, aged 45.	Heart enlarged. Blood-pressure 200.	Red cells 6,575,000. Hemoglobin 125. Color index 0.95.	
138.— Geisbock	Male, aged 46.	Heart enlarged. Blood-pressure 220. Trace of albumin in urine.	Red cells 6,000,000. Hemoglobin 112. Color index 0.93.	
139.— Geisbock	Male, aged 51.	Heart enlarged. Blood-pressure 250. Arteriosclerosis. Contracted kidney; albumia and casts in urine.	Red cells 5,700,000. Hemoglobin 104. Color index 0.91.	
140.— Geisbock	Male, aged 51. Admitted with cerebral hemorrhage.	Red face. Heart slightly enlarged. Blood-pressure 195. Albuminuria.	Red cells 5,700,000.	
141.— Hess	Female, aged —. Complaints of headache, giddiness, palpitation, buzzing in ears and occasional slight bleeding from mucous membranes.	General cyanosis. Slight emphysema. Heart slightly hypertrophied. Distention superficial veins. Blood-pressure 190. A little albumin and a few hyaline casts.	Red cells 7,500,000. Hemoglobin 180. White cells 19,000. Differential normal. No nucleated red cells. Color index 1.20.	
142.— Mohr	Female, aged 42. Complained of dyspnea and palpitation.	Marked cyanosis. Heart enlarged, especially to left; vessels slightly sclerosed. Blood-pressure 310. No albuminuria.	Red cells 7,750,000. Hemoglobin 140. White cells 4,000. Color index 0.9.	These two cases (142 and 143) mentioned in medical journal only as short society abstracts without any further details.

143.— Mohr	Male, aged 27. Chief complaint, nervous disorders.	Cyanosed. Blood-pressure 190 to 200. Retinal veins dilated. No albuminuria.	Red cells 6,900,000.	Treatment blood-letting and inhalations of oxygen.
144.— Brill	Female, aged 60; Russian Jewess; married. Four children. Measles and small-pox in infancy. "Kidney disease" 20 years ago (in bed a few weeks and regained complete health). Four years ago attacks of headache, dizziness and ringing in ears and soon after swelling left side. X-ray slightly improved general condition but had no effect on blood. Last year symptoms returned with same intensity and spleen grew rapidly. Liability to bleeding from gums, edema legs and eyelids and constipation. Hemorrhoids and emaciation.	No cyanosis, although tongue deep red and palms livid. Spleen extended into pelvis (see "Remarks"). Liver considerably enlarged, smooth and tender. Epigastric veins distended. No ascites. Lungs emphysematous. Rough systolic apical murmur but no clinical signs of cardiac disease. Pulses equal, regular and of increased tension. Blood-pressure 155. Visible episternal pulsation. Slight enlargement left submaxillary lymph-node. Emaciation. Arcus senilis. Tenderness over sternum and tibia. Chronic nephritis. Proctodentia uteri and marked atlatation and thrombosis of hemorrhoidal veins, with prolapse of rectum. Reddish color. Spleen shows percussion enlargement. Heart not enlarged. Blood-pressure 192 to 220. Reddish color. Spleen shows percussion enlargement. Heart slightly enlarged to the left. Blood-pressure 165. Liver slightly enlarged. Trace of albumin and sugar in urine. Red face. Spleen shows percussion enlargement. Liver slightly enlarged. Heart slightly enlarged. Blood-pressure 160. Pulse 83. Blood-pressure 152.	Three years ago red cells 8700,000. Hemoglobin 105. White cells 14,500. Polys. 80 per cent.; L. lymph. 11 per cent.; S. lymph. 8 per cent.; myeloc. 1 per cent. Last year red cells, on 21 counts, varied from 5,400,000 to 9,680,000. Hemoglobin, on 38 counts, from 88-145. White cells, on 16 counts from 7,500 to 45,200. Polys. 68 per cent.; L. lymph. 7 per cent.; S. lymph. 10 per cent.; cosin. 3 per cent.; myelo. 4 per cent.; mononc. 7 per cent.; trans. 3 per cent. Red cells 5,500,000 to 6,000,000. Hemoglobin 112-117. Red cells 5,800,000. Hemoglobin 155. Color index 1.34.	Splenic enlargement materially increased from September last, when most of anterior border of spleen was at the umbilicus, to present time when right border reaches right mammary line. Brill calls attention to the absence of cyanosis, notwithstanding the erythrocytosis of between eight and nine million, as well as to the accompanying leukocytosis which he thinks may suggest a leukemia of the myeloblastic type. He also calls attention to the low percentage of hemoglobin.
145.— Staehelin	Female, aged 50. For two years has complained of nervousness, sleeplessness and heat in head.			
146.— Staehelin	Male, aged 57. Neuralgia for one year.			
147.— Staehelin	Male, aged 52. Face was always red. Palpitation of heart after a full meal.			
148.— Rover, aged 50.			Rover's article presents the findings in two new cases of polycythemia studied with the hemodynamic method, the findings being tabulated under twenty-two headings and showing how the circulatory conditions differ in different patients and in the same patient at different times.
149.— Rover, aged 44.			Rover's article also teaches that high saturation of the venous blood with oxygen is of evil import in polycythemia as well as in other disease.

*For references see text.

TABLE 5 (CLASS E).—CASES CONSIDERED DOUBTFUL, EITHER ON ACCOUNT OF INSUFFICIENT DATA, APPARENT DUPLICATION OR FOR OTHER OBVIOUS REASONS

Case No. and Author*	History	Examination	Blood Examination	Outcome, Treatment, Autopsy and Remarks
150.— Dronke and Ewald	Great polycythemia following long continued use of Leveico water, which contains iron and arsenic.		Red cells in December, 1891, slightly over 5,000,000. In January, 1892, red cells 8,400,000 and hemoglobin 85.	Last count carefully verified by a second count. Note low hemoglobin percentage.
151.— Neumann	Male, aged 57. Supposed to have acute Addison's disease with great anemia. Gradual improvement, oligocythemia giving way gradually to polycythemia and later the number of red cells falling to normal.		Red cells in April, 1885, 1,120,000. Gradually increased, reaching 7,700,000 in following January and falling to 5,000,000 in July.	Weber, referring to this case, says: "It is probable that in all cases of anemia from hemorrhage, and other forms of anemia improving without special treatment, the anemia may occasionally give way to temporary polycythemia, as if normal level had been overshoot by reaction of the blood making organs."
152.— Guinon, Rist and Simon	Female, aged 10. Chronic jaundice of variable degree with urobilinuria and splenomegaly. Transitory cyanosis and polycythemia accompanied exacerbation of jaundice.	Transitory cyanosis. Spleen enlarged.	Red cells 6,000,000 to 7,600,000. A few months later fell to 4,000,000 while a year previous had been 3,400,000. Resistance to hemolysis above average.	Weber thinks this case may be compared in some respects to Hayem's chronic splenomegalic acholuric jaundice with oligocythemia. Compare also with Mosse's case (Number 159).
153.— Reckzeh	Male, aged 24. Progressive compression superior vena cava by malignant tumor of the thymus. March, 1904, face and neck began to swell; pain in abdomen and chest, cough and expectoration.	(Cyanosis limited to territory of superior vena cava until well towards end of life. Spleen enlarged. Veins enlarged. Edema eyelids. Dyspnea. Cervical glands enlarged. Liver not enlarged.)	Red cells upper part of body 5,400,000 to 6,700,000; lower part of body from 4,400,000 to 6,000,000. White cells 6,900 to 15,000 upper part of body and 8,100 to 12,000 lower part.	Died with increased dyspnea, edema, venous dilatation, weakness and mental stupor. Autopsy: Tumor of thymus had extensively involved right lung (possible cause of polycythemia), with metastatic growths in brain, kidneys, pancreas and elsewhere. Spleen soft and dark red. Bone marrow apparently not examined.
154.— Reckzeh	Male, aged 58. For four years headache, dyspnea, palpitation and poor sleep. Symptoms gradually became worse and in December last complained of pain and swelling of liver and of diarrhea. Is still in the same condition. Does not drink. Dies venereal infection.	"Patient is a strong man." Moderately cyanosed. Spleen not mentioned. Complains of swelling of liver. Peripheral vessels sclerosed. Urine shows some albumin and a few hyaline casts.	Red cells, on three counts in January, 1905, from 10,000,000 to 10,800,000. White cells 10,000. Polymorphonuclear neutrophils 73 per cent.	This case appears to be identical with Kraus' case (Number 26) and is therefore included in doubtful class to avoid duplication.
155.— Koranyi	This case referred to by Bence as having been treated by oxygen inhalations. No particulars.			

156.—
Hirse-
feld
Male, aged 51. Left sided hemo-
thorax. The blood not examined
during life.
Spleen enlarged.
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Autopsy: Spleen enlarged and con-
tained cyst with sero-sanguinous
contents. Splenic substance showed
partial myeloid transformation
(leukoblastic, not erythroblastic).
Very many cells containing phago-
cytes were present. In spite of large
pleural hemorrhage, viscera ex-
tremely engorged. Bone marrow
long bones mostly red and micro-
scopically showed proliferation of
cellular elements (notably normo-
blasts and giant cells but not mast
cells).
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157.—
Niklaum
Female, aged 20. Splenomegaly from
early childhood. Cyanosis from age
of 13. Commenced to suffer from
various hemorrhages at 15. At 17
acquired malaria. Her sister also
had enlargement of spleen from
childhood.
Male, aged 33. Lues eleven years ago.
Repeated attacks of paroxysmal
hemoglobinuria.
Cyanosis. Spleen enlarged.
Polycythemia present.
.....
Pel suggests that both the polycyth-
emia and the paroxysmal hemoglo-
binuria may have been of toxicemic
origin.
Mosse suggests case compares in some
respects with cases of polycythemia
with splenomegaly and in other re-
spects with Hayem's chronic infec-
tious splenomegalic jaundice with
urobilinuria (without bilirubin-
uria) and with oligocythemia.
Mosse's case may also be compared
with Guinon, Rist and Simon's case
(Number 152).
Note that in this case there was prac-
tically no increase of red cells al-
though hemoglobin percentage was
high.

158.—Pel
Red cells 6,000,000 to 9,000,-
000. Hemoglobin 110-140.
.....
Red cells 6,750,000 to 7,825,-
000. Hemoglobin 100-110.
.....
Red cells 4,290,000 to 4,800,-
000. Hemoglobin 120. White
cells 11,100. Blood flows
freely. Many poikilocytes.
A few macrocytes and some
nucleated red cells. All cells
overstain very markedly.
Skin markedly livid, especially face.
Spleen enlarged. Obvious inspira-
tory dyspnea. Heart slightly di-
lated and an occasional systolic
murmur at tricuspid orifice. Pulse
rapid, small and compressible. No
edema. Urine shows slight trace of
albumin. Height 5 feet 3 inches.
Weight 86 pounds.

160.—
Anders
Female, aged 21. Neuropathic hered-
ity. Malaria at age of 12. Appendec-
tomy at 17. At 19 struck by hard
ball over right ovary; followed by
three abscesses which ruptured into
the uterus and was followed by cyst-
itis. Two years later curetment.
Later acute nephritis. Menses irreg-
ular and somewhat painful. Present
trouble dates to operation for ap-
pendicitis although no cyanosis un-
til curetment. Patient weak and
neurasthenic.

*For references see text.

TABLE 5.—(Continued)

Case No. and Author*	History	Examination	Blood Examination	Outcome, Treatment, Autopsy and Remarks
161.— Schneider	Male, aged 51. Formerly had malaria: In April, 1901, found to have polycythemia and splenomegaly. Spleen removed in May, 1901. Signs of pneumonia in Dec. 1901, followed by progressive pulmonary tuberculosis. Died in October, 1902. Not clear that this is a case of erythremia.	Spleen enlarged. Patient corpulent.	In April, 1901, red cells 6,000,000, white cells 22,000. In June, 1901, red cells 4,500,000, white cells 16,000. In April, 1902, red cells again above normal. In October, 1902, red cells 1,385,000, white cells 55,400. Myelocytes 1.4 per cent, and twice as many nucleated red cells as white cells.	The removed spleen contained anemic infarcts; capsule thickened from old perisplenitis, but no careful examination made. Autopsy: Advanced pulmonary tuberculosis. Dilatation and hypertrophy both sides of heart. Myocardial fibrotic changes in left ventricle. Aortic atheroma. Nephritis. Ulcer pyloric region of stomach. Marrow of long bones red.
162.— Turk	Patient exhibited by Turk showing high grade of polycythemia, cyanosis and splenomegaly.	Cyanosis of high grade. Spleen greatly enlarged.	Red cells 9,500,000 Hemoglobin 180. White cells 27,000.	This appears to be a case exhibited before a society and, as it was probably later included by Turk in list of cases published in 1903, it is included in this class to avoid duplication.
163.— Hall	Female, aged 40. Patient very neurotic.	Marked cyanosis of face and extremities. Spleen greatly enlarged.	Red cells 8,400,000 to 9,935,000. Hemoglobin 170. White cells 6,500 to 22,000. Viscosity greatly increased.	Hall says that the notes on this case were given him by Turk, but without any history. It seems probable that it is a duplication of one of Turk's cases and it is therefore included in this class to avoid repetition.
164.— Blumenthal	Female, aged 31. From two years of age subject to attacks of paroxysmal dyspnea, accompanied by severe headache and followed by copious expectoration. From age of 21 cyanosis, debility and hemorrhages.	Cyanosed. Heart somewhat hypertrophied; tachycardia. Retinal veins tortuous and engorged with blood. Exophthalmos.	Red cells 11,450,000. Hemoglobin 110. White cells 16,300. Myelocytes 36 per cent. No nucleated red cells.	Blumenthal regarded this case as congenital. Autopsy: Bronchopneumonia; bone marrow red and succulent; leukoblastic tissue markedly in excess of erythroblastic.
165.— Holmes	Male, aged 21. Father died at age of 57 from some abdominal disease. While in school patient became weak, dizzy and nervous and after a few months had to go home. He was troubled with diarrhea and constipation and was treated for mucous colitis. Improved somewhat but attacks of abdominal distress continued. One of the attacks was accompanied by so much tenderness over the appendix that the family physician recommended its removal, which was done.	No cyanosis remembered. Spleen not noticeably enlarged. No clubbing of fingers remembered.	Red cells before operation 7,750,000. Two months later had fallen to normal.	Many blood counts showed a high grade of polycythemia without apparent abnormality in the white blood-count. Polycythemia disappeared entirely shortly after removal of appendix and six months later the patient seemed improved in general.

166.—

Fells

Female, aged 37. Long resided in India and had suffered from sun-stroke and many attacks of fever. In 1901 returned to England and began to complain of shivering attacks accompanied by pain in the left side and radiating down leg. In 1906 had intermittent pyuria with pyrexia. Had been accustomed to taking sulphonal for years, although none had been prescribed during the nine months prior to her death.

Male, aged 53. Obesity with extreme tendency to drowsiness.

167.—

Munzer

(Cyanosis present. Spleen and liver normal. Distention of the neck (see "Remarks").

Munzer regarded this as a case of erythrocytosis, probably from blood stasis not of cardiac origin. There was distention of the neck which Munzer supposed to be connected with substernal fat or goiter. Under thyroid treatment the patient's weight fell from 103 to 89.3 kg. and all alarming symptoms disappeared.

168.—

Howard

Female, aged 47; married; native of the United States. Both parents died of apoplexy. Patient always robust and high colored. Menstrues every three weeks and lasted seven or eight days. For five years dyspnea on exertion and occasional attacks of palpitation. Three attacks pneumonia during past three years; since last attack a year ago dyspnea constant and at times severe. Past six months swelling of legs and pain around the heart. During last month several attacks of numbness and stiffness of right arm, left side neck and left arm.

Only cyanosis observed was occasional appearance of bluish tint to lips; face was flushed. Spleen never perceptibly enlarged. Lungs slightly emphysematous. Heart dulness increased but sounds clear and strong. Radial arteries stiff. Blood-pressure 190. Urine shows trace of albumin.

Red cells 5,124,000 to 8,670,000. Hemoglobin 70-130. White cells 8,000 to 40,000. Polys. 70-86 per cent.; Lymph. 1.2-18 per cent.; L. mono. 0.7-9.4 per cent.; Trans. 2-9 per cent. Eosin. 0.6-1.00 per cent. Masts 0-1.4 per cent. Stimulation forms present at times and erythroblasts twice. Anisocytosis; poikilocytosis and polychromatophilia noted at times. Color index 0.46-1.07.

Red cells 6,500,000. No leukocytosis.

Eventually the patient died with increase of myasthenia and paralysis. No autopsy. Fells considered this case one of auto-intoxication from the alimentary tract.

* For references see text.

TABLE 5.—(Continued)

Case No. and Author.	History	Examination	Blood Examination	Outcome, Treatment, Autopsy and Remarks
169.—Weber	Male, aged 22. Cyanosis existed at birth; there seemed to be a patency of the interventricular septum. During the early years of his life often had attacks accompanied by exacerbation of the cyanosis which seemed sometimes to be induced by a slight knock or annoyance. Could not walk until 4 years old. Subject to enuresis. Father and mother healthy. Twin brother well and strong.	Great cyanosis lips, nose, tongue, ears, hands and feet; tongue and lips bluish-black. Liver, spleen and lungs normal. Heart: slight systolic murmur. Blood-pressure 100. Gums bleed easily owing to decayed teeth. Urine shows well marked cyclic albuminuria. Great clubbing of fingers and toes. Impaired capillary circulation in hands shown by long persistence of white marks left by pressure. X-ray shows heart enlarged transversely and some widening of aortic shadow to the left. Cyanosis present. Spleen enlarged.	Red cells 10,300,000. Hemoglobin 160. White cells 7,000. Polys. 72.2 per cent.; Lympho. 17.2 per cent.; L. hyaline 22.0 per cent.; Eosin. termed. 5.4 per cent.; Eosin. 2.0 per cent.; Masts 1.0 per cent. Red cells appeared normal. Blood very dark colored.	
170.—Loewy	Middle aged merchant. Loewy does not give detailed account and says that this case will be reported elsewhere by Senator.		Polycythemia present; no deformities. Hemoglobin 204. Blood was taken from median vein and amount of iron in same found to be 115.6 mg.	Remained at hospital three months. Treatment by venesection showed a little improvement. Not seen again.
171.—Comessatti	Male, aged 28; workman. First complained eight days ago of headache and heaviness in head and of rigidity of the neck and marked vertigo. Three days later developed unilateral paresis of left side with some aphasia and transitory diplopia and difficulty in swallowing.	Cyanosis not mentioned. Spleen not enlarged. Heart: left ventricle hypertrophied; galloping rhythm. Temporary diplopia. Bilateral nystagmus; slight strabismus. Muscular spasms on right side. Tendon reflexes increased. Urine negative.	Red cells, on four counts, 6,200,000 to 7,200,000. Hemoglobin 95-100. White cells 8,400 to 16,500. Polys. 76 per cent. Lymph. 16-22 per cent. Mono. 4-7 per cent. Eosin. 1 per cent.	
172.—Lange	Male, aged 55. Has had gout. About a year ago developed weakness of memory. Two weeks before coming to hospital had attack of unconsciousness. After that trouble with speech, heavy gait and weakness left hand.	Face red. Spleen not enlarged. Heart enlarged to the left. Urine contains five per cent. of sugar, but no albumin.	Red cells 7,020,000. Hemoglobin 100.	Note sugar in urine.

173.— Lange	Male, aged 64. Has had several apoplectic attacks during last few years, the last one this Spring, since which time has had left sided body weakness, with weakness right hand and right angle of mouth; also weakness of memory and uncertainty of speech. Female, aged 60. Palpitation of heart and lumbago.	Spleen not enlarged. Heart enlarged to left. Arteries tense and tortuous. Lowered Babinski; increased patellar reflex. Urine shows a few granular casts and a trace of albumin.	Red cells 6,400,000. Hemoglobin 100. No alteration in stained blood picture.	
174.— Stachelin		Bluish red color. Spleen and liver not enlarged. Heart trouble present. Blood-pressure 176. Urine shows trace of albumin. Cyanosis not mentioned. Spleen palpable. Liver slightly enlarged. Lungs emphysematous. Heart slightly enlarged to the left. Blood-pressure 185. Trace of albumin in urine. Cyanosed. Neither spleen nor liver enlarged. Heart trouble present. Blood-pressure 140. Cyanosed. Neither spleen nor liver enlarged. Lungs emphysematous. Heart slightly enlarged to the left. Much albumin in urine. Blood-pressure 215. History lost.	Red cells 7,800,000. Hemoglobin 155. Red cells 8,500,000. Hemoglobin 238. Red cells 7,600,000. Hemoglobin 155. Red cells 8,500,000. Hemoglobin 194. Red cells about 8,000,000.	Stachelin considers this a case of secondary polycythemia. Stachelin considers this a case of secondary polycythemia resulting from emphysema and nephritis. Stachelin considers this a case of secondary polycythemia resulting from cardiac stasis. Stachelin considers this a case of secondary polycythemia as result of emphysema and nephritis. Stachelin mentions this case and says that the history of the case has been lost. Regarded by authors as primary tuberculosis of the spleen.
175.— Stachelin	Male, aged 55. For five years headache, vomiting, pain in gastric region, palpitation of heart and pain in back.			
176.— Stachelin	Female, aged 47. Dyspnea, congestion of head, vertigo and headache.			
177.— Stachelin	Female, aged 40. Headache and angina.			
178.— Stachelin	History lost.			
179.—Collet and Galavardin	A case of massive tuberculosis of the spleen thought by the authors to resemble clinically cases of splenomegalic polycythemia.	Spleen enormous.	No blood count made but general physical features of blood similar to cases of erythremia.	

* For references see text.

TABLE 6 (CLASS F).—THE JOURNALS IN WHICH THE FOLLOWING CASES WERE REPORTED WERE SECURED TOO LATE TO PERMIT OF TRANSLATION OF THE FOREIGN ARTICLES OR FOR THE INCLUSION OF ANY OF THE CASES UNDER THE PROPER CLASSIFICATION

Case No. and Author*	History	Examination	Blood Examination	Outcome, Treatment, Autopsy and Remarks
180.— Wasser- thal	Male, aged 28; merchant. A case in which dyspeptic symptoms predominated.	Red cells 7,400,000 to 7,500,000. Hemoglobin 100. White cells 11,000.
181.— Umber	Male, aged 56.	Blood-pressure 138-145. Cyanosis present.	Red cells 11,960,000. Hemoglobin 150. White cells 14,400. Color index 0.63.
182.— Umber	Female, aged 50. Case complicated by diabetes.	Spleen and liver enlarged. Blood-pressure 115. Urine shows albumin, casts and 1 per cent. of sugar.	Red cells 10,880,000. Hemoglobin 150. White cells 5,700. Color index 0.63.
183.— Jones	Male, aged 56; English. For many years severe attacks of migraine. Fifteen years ago edema of ankle and leg; was organically sound and treatment caused disappearance of edema and improvement in migraine. Four years ago sudden attack of vertigo and loss of consciousness for about one minute. At intervals since has been giddy. For several years color intensified. Some constipation and slight dyspnea on exertion.	Extreme general cyanosis, most marked in ears and lips, which were nearly black. Also marked in mucous membranes. Gums, tongue, pharynx and inside of mouth all of deep purple color. Spleen: extended nearly to pubes; not tender; surface smooth and firm. Lungs: nothing abnormal beyond a few coarse rhonchi. Heart: soft systolic apical murmur without symptoms. Conjunctivae deeply injected. Gums bleed easily. Blood-pressure 140-160. Urine: a faint trace of albumin.	Red cells 8,500,000. Hemoglobin 110. White cells 20,000. Color index 0.6. Polys. 92 per cent.; small lymph. 6 per cent.; large lymph. 1.2 per cent.; eosinophils 0.8 per cent. No poikilocytes, mast cells or myelocytes.	Treated with iodid in form of iodalbin gr. v t. d. s., for a month at a time with a week's intermission. He was first seen in March, 1911, and last seen in Oct., 1911, at which time his health was still good, the cyanosis not so marked, the spleen possibly slightly smaller, the cardiac condition satisfactory, the murmur giving rise to no symptoms, and the lungs perfectly normal.
184.— Voorsanger	Female, aged 19; stenographer. Entered hospital Oct. 9, 1911, complaining of pain in cardiac region for past two years, cyanosis for about one year and weakness for past six months.	Marked cyanosis of skin, lips and mucous membranes. Spleen and liver not enlarged. Lungs negative. Heart somewhat enlarged; tones pure. Patellar and plantar reflexes increased. Eye grounds negative. Urine negative. Faeces and sputum negative. No glandular enlargement.	Red cells 7,920,000. Hemoglobin 120-140. White cells 8,400. Polys. 71 per cent.; large lymph. 23 per cent.; large mononuc. 6 per cent.; eosin. 0 per cent.	Von Pirquet was negative. X-ray showed considerable enlargement of heart to the right.

185.—

Abrahamson

Male, aged 30. Entered hospital complaining of shortness of breath and intense cyanosis of upper half of trunk.

Intense cyanosis upper half of trunk. X-ray examination of the chest showed a mediastinal tumor.

Red cells from the ear 10,000,000; from the toe only 5,000,000.

This case was referred to by Dr. Abrahamson in the discussion of Dr. Voorzanger's paper as illustrating the difficulty of differentiating true polycythemia from local polycythemia. Autopsy showed tumor to be a sarcoma pressing on the vena cava, which was undoubtedly the cause of the local polycythemia.

186.—

Hamilton and Morse

Female, teacher. Ordinary diseases of childhood, including scarlet fever at 16, followed by "chronic gastritis." In 1908 indigestion and acne. In Spring of 1909 attack of "grip" and noticed increase in size of waist and "tanned" appearance of skin. In Nov., 1909, severe attack indigestion with extreme constipation. Menses ceased in Aug., 1909; since then frequent nose bleed.

Skin yellowish and at times markedly cyanotic. Spleen reached to point halfway between costal margin and umbilicus. Liver reached halfway to umbilicus. Lungs and heart apparently normal. Sclera slightly tinged with yellow. Herpes zoster on right side; vaginal and rectal examination negative. Urine normal except for slight trace of bile.

Red cells 7,408,000 to 8,000,000. Hemoglobin 85-95. White cells 8,400 to 9,400. Polys. 80-82 per cent.; small mononuc. 10-14 per cent.; large monos. 4 per cent.; transit. 1-3 per cent.; eosinophils 1-3 per cent. Slight poikilocytosis. Red cells stain lightly. A few microcytes. No nucleated reds. Platelets not increased.

Treatment with tonic baths, increasing doses of K I and carefully chosen diet caused some decrease in size of liver and some general improvement, as did also x-ray, massage and out door exercise. On March 17, 1910, patient vomited six quarts of blood in four hours and died with signs of acute hemorrhage and collapse. Autopsy: Showed marked evidence of hyperplasia of red cells in the bone marrow, evidence of blood formation in spleen, liver and retro-peritoneal lymph-nodes and marked cirrhosis. Death apparently due to esophageal hemorrhage.

187, 188 and 189.—
v. Bergman and Plesch

Tabulated findings given in three cases of polycythemia. Examined with same detail as Senator's patient.

.....

Authors inclined to regard the polycythemia as compensatory in some cases.

*For reference see text.

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VERRUGA PERUVIANA AND ITS COMPARATIVE STUDY IN MAN AND THE APE *

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The fact that the Panama Canal is to be opened shortly calls our attention to a disease that may be of more or less interest and importance to Americans in the next few years. Even before the Spanish occupation of South America a peculiar sickness was endemic over a certain inland portion of Peru. The Spaniards suffered terribly from its ravages, as have the natives since then, and the trouble is still present in this same region. At the time of the building of the Oroya Railroad through this country in 1871, the workmen were afflicted greatly with a severe fever termed Oroya fever, and from Verruga peruviana. Clinicians finally began to have the feeling that the two diseases were one and the same, though in a different type, and in 1885 a young medical student, Daniel Carrion, allowed himself to be inoculated with the blood of a patient suffering from the latter affection, and in thirty-nine days he was dead from a typical attack of Oroya fever.¹ The heroic young man apparently settled all doubt as to the entity of the two diseases; though, as I will mention later, the question is once more under discussion.

Through a peculiar happening the Berne Dermatology Clinic had what was probably the only case of this trouble ever seen in Europe in the person of a Swiss mountain guide from Zermatt. In 1909, along with a companion, he assisted Miss Annie E. Peck² in climbing Huascarán Mountain in Peru. Through misfortune on their way down they were forced to stop twelve days on the ice fields, and his companion had his hands and feet so badly swollen that the two guides were forced to remain some time in Peru before their return to Switzerland.

About one week after his arrival in Zermatt the patient began to notice fleeting symptoms of an uncomfortable feeling, followed by sweating, when in a hot room. They only lasted five or ten minutes, and he was not aware of any temperature disturbance. A little later he noticed a small growth on his left leg and shortly afterwards quite a few came

*From the Dermatology Clinic in Berne, Switzerland (Director, Professor Dr. Jadassohn).

1. For the history, clinical symptoms, etc., of this interesting disease, I have drawn largely from the complete and well written monograph of Prof. Ernesto Odriozola; "*La Maladie de Carrion*" ou "*La Verruga Péruvienne*," Paris, Georges Carré, et C., Naud, 1898.

2. Peck, Annie E.: Harper's Monthly Magazine, January, 1909.

out on his face, arms and hands, and the patient on advice consulted Prof. Jadassohn in the Berne Clinic. He had had no other symptoms, and on admittance to the hospital seemed to be perfectly well; except for the tumors. I will not go into detail of what has been already described,³ but suffice it to say that thorough physical examination showed absolutely nothing pathological outside of the cutaneous growths. The blood-picture was absolutely normal, the Wassermann reaction negative and the von Pirquet cutaneous test for tuberculosis and subcutaneous injections of tuberculin in varying amounts up to 1.0 mg. also showed nothing. Some of the tumors were excised for histological examination and inoculation experiments, others were treated with carbon dioxid snow, pyrogallic ointment, tincture of iodine, etc., and in about three weeks it was impossible to prevail on the patient to remain any longer in the hospital, as he was feeling perfectly well and the lesions had practically healed. And since his departure occasional reports show that, outside of a few rheumatic symptoms, he has been quite well.

ETIOLOGY

The mountain climbers on their trip had just touched the edge of the verruga territory, but it was apparently enough to transmit the infection. The disease is limited to an inland portion of Peru, from 28 to 60 kilometers from the seaboard. The country is quite mountainous in character, varying in altitude from 400 to 3,000 meters. Curiously enough, the present limits of the disease are somewhat smaller than at the time of the Spanish occupation. The valleys are deep and hot, while the streams are sluggish and many swamps abound. Odriozola thinks that the climate may have some etiological importance; while the water is blamed by others. However, cases have been known to occur in patients who have used nothing but potable water, and, moreover, in April,⁴ when the water recedes, the verruga cases augment. No race, age or sex is spared, and Odriozola says that the horses, mules, dogs, llamas, chickens, etc., have symptoms closely allied to those of the human beings. Cases have been cited where the patients have staid but one-half an hour or an hour in the verruga territory and there is at present a feeling that, as in many other tropical diseases, some insect may have something to do with the transmission of the disease. The affection is inoculable, though not contagious, and it is apparently transmissible by the placenta. The incubation period varies from fifteen to forty days, or even longer. In Carrion's case it was twenty-one days, perhaps due to the fact that he was inoculated intravenously; while in Jadassohn's patient it was at least sixty days. Apparently one attack gives immunity for the rest of life.

3. Jadassohn, J. and Seiffert, G.: Ein Fall von Verruga peruviana, gelungene Uebertragung auf Affen. *Ztschr. f. Hyg. u. Infektionskr.*, 1910, lxvi, 247.

4. Brault, J.: La Verruga du Pérou. *La Pratique Dermatologique*, iv, 832.

SYMPTOMS

In the severe type of the affection, the so-called Oroya fever, the disease is usually ushered in with a chill accompanied by a fever; after prodromal symptoms of headache, general malaise and pain in the joints and muscles.⁵ The fever may go up to 40 C. (104 F.), or even higher, and is accompanied by nausea, vomiting, rapid anemia, sleeplessness, vertigo, hemorrhages, coma and death. The glands are enlarged and the liver and spleen engorged. If the termination be good, the temperature gradually falls and the symptoms lessen. The fever is either remittent, intermittent or irregular in type and may accompany, precede or follow the appearance of the cutaneous manifestations. The pulse is frequent, soft, compressible and, even with a temperature of normal, it may be 120 to 140, or even higher. Among the types of hemorrhage, enterorrhagia is rare, and usually comes along towards the termination of the disease, being an unfavorable prognostic sign. Epistaxis is a very common symptom and petechiae are frequent. Sweating is profuse, especially in the fever of an intermittent type. Edema of the toes and legs is generally found, though it is rarely generalized except in the grave cases. Nervous symptoms of vertigo, syncope, cephalalgia, delirium, insomnia and hic-cough are sometimes seen.

Pneumonia, enteritis, enterocolitis and hemorrhages are among the complications most frequently encountered; though several cases of verruga meningitis have been reported. Occasionally malaria and verruga are seen in the same patient at the same time.

ERUPTION

The cutaneous eruption is of two general types: "*miliaire*"⁶ or tuberculous, and "*mulaire*" or nodular. Under the first a tubercular, a sud-aminal, a vesicular and a pustular efflorescence are noted. The eruption may be localized, generalized, discrete or confluent, and the favorite seats with the tubercular or "*miliaire*" efflorescence are the anterior regions of the legs, extensor surfaces of the forearms, antero-extensor surfaces of the arms, forehead, jaws, nose, eyebrows, knees and elbows. The mucous membranes of the eyes, mouth, digestive and genito-urinary tracts are also frequently involved. Moreover, verruga nodules have been found in the peritoneal coats, spleen, liver, pancreas, kidneys, lungs, muscles, and central nervous system. The "*mulaire*" or nodular lesions are subdermic, varying in size from a walnut to a small orange, and they may be sessile

5. Prof. Odriozola proposes to divide the disease into two types, according as the fever or as the cutaneous tumors predominate in the symptoms. The first type he would call "Oroya fever" or "*Fièvre de Carrion*," and the latter "*Eruption de Carrion*"—thus naming the disease after the young martyr.

6. The words "*miliaire*" meaning tubercular and "*mulaire*" meaning nodular have been taken over bodily from the Spanish by Prof. Odriozola.

or pedunculated. They are never internal and are found on the eyelids, cheek-bones, lobules of the ears, bridge of the nose and the knees. Jadassohn's patient had examples of both the "*miliaire*" and the "*Mul-
aire*" efflorescences—confined mostly to the face, arms and legs. The conjunctiva of one eye was affected, but otherwise the mucous membranes showed nothing. The patient also showed a macular eruption resembling a lupus and thus far not described in connection with *verruca peruviana*.

PATHOLOGY AND BACTERIOLOGY

In regard to the pathology and bacteriology of the disease, much still remains to be desired, because of the marked differences in the findings of investigators. The blood-picture is that of a rapid and marked anemia. Bassett-Smith⁷ found an abundance of nucleated red cells, and the erythrocytes were irregular in their size, shape and staining qualities. Many basophilic granulations were seen and a few myelocytes were present. The bone-marrow usually shows signs of proliferation. The liver and spleen are generally engorged and the latter organ occasionally extends down to the iliac fossa. It is soft and more or less friable, while the liver is slaty in color, as in malaria, due to the destruction of red cells. The lymphatic ganglia are greatly engorged; those of the mesentery occasionally reaching the size found in tuberculous peritonitis and leukocythemia. The urine is merely febrile. Histologically, Nicolle⁸ found small nodules of epithelioid cells in the liver and lungs, but no caseation. In the lymph-nodes he found true caseation in their centers, but no giant cells. Somewhat analogous though more marked lesions were noted in the spleen. DeVecchi⁹ found early hemorrhagic lesions in the spleen, lungs, liver, muscles and skin along with new tissue formation. In the liver there was a vacuolization of the elements and compression of the cells by the widening of the vessels and by the formation of verruca nodules. Pigment clumps were also noted and phagocytic leukocytes were noted in both the liver and spleen. He found giant cells in both these organs and in the lungs there were appearances of new tissue formation and small areas of bronchopneumonia. The cutaneous lesions have been studied by several men and it seems to be the consensus of opinion that they are granulomatous in type; made up of fibroblasts, mono- and polymorphonuclear leukocytes, plasma and red cells. The tumors are very vascular and later show signs of necrosis. Acid-fast bacilli have been found in the internal lesions by Nicolle,⁸ and also by

7. Bassett-Smith, P. W.: The Pathology of the Blood in Verruca. Brit. Med. Jour., Sept. 18, 1909.

8. Nicolle, C.: Note sur la bactériologie de la verruca du Pérou. Ann. d. l'Inst. Pasteur, 1898, xii, 591.

Letulle,¹⁰ Escomel,¹¹ Giltner¹² and Izquierdo,¹³ while just lately an organism closely related to the paratyphosus bacillus, type B, has been found by DeVecchi,⁹ Barton,¹⁴ Biffi¹⁵ and others. Cell inclusion-bodies have also been reported.

DIAGNOSIS

In diagnosis one must always keep malaria in mind, for in fact the two diseases have been very frequently confused, and they are occasionally found together in the same patient. Typhoid fever and the blood-picture will serve to differentiate them. However, the therapeutic test must also be ruled out. In a patient having the cutaneous tumors as the predominant symptom it would also be necessary to think of neurofibromatosis (von Recklinghausen's disease). The affection occurring in a tropical country, framboesia and *Bouton d'Orient* would likewise have to be considered in a differential diagnosis. In the former, suitable examination for the specific spirochete would be sufficient, while in the latter there would be the history of painless ulcers on the exposed parts, in which proper examination would reveal the Leishmann-Donovan bodies.

PROGNOSIS AND TREATMENT

The prognosis of verruga should always be guarded, though the cases having the cutaneous tumors as their main symptom usually do better than the ones with the high fever.

The treatment is symptomatic and apparently of little avail. Quinin and the salicylates have been the drugs mostly relied on and it will be interesting to see what will be the effect of our new drugs, salvarsan and neosalvarsan. Perhaps they will be as effectual as in framboesia, and their use is to be recommended—at least as an experiment. Despite all treatment the cutaneous lesions usually last from four to six months, and even up to two years. In the Berne case the growths were practically all gone in a space of three months.

9. DeVecchi, B.: Ueber die Verruga peruviana. Arch. f. Schiffs u. Tropenhyg., 1909, xiii, part 4, 143.

10. Letulle: Histological Study in Prof. Odriozola's monograph (Note 1).

11. Escomel, E.: Anatomie pathologique du verrucome de Carrion. Ann. d. dermat. et d. syph., 1902, iii, 961.

12. Giltner, H. A.: Verruca Peruana or Carrion's Disease. Jour. Am. Med. Assn., 1911, lvii, 2074, Abstr., München. med. Wchnschr., 1912, No. 8, p. 440.

13. Izquierdo, V.: Spaltpilze bei der Verruga peruviana. Virchow's Arch. f. path. Anat., 1884, xcix, 411.

14. Barton: Quoted by DeVecchi (Note 9).

15. Biffi y Carbajal: Verruga peruviana und schweres Fieber Carrion. Arch. f. Schiffs u. Tropenhyg., 1908, Part I. Quoted by DeVecchi (Note 9).

EXPERIMENTAL TRANSMISSION

Outside of one experiment mentioned by Odriozola¹ on page 175 of his book, no attempt has ever been made to transmit the disease to lower animals. In this case a bitch was inoculated with the blood from a large verruga tumor. Later she had several growths on the paws and ears, delivered two dead pups and died. The experiment was rather indefinite, and no autopsy was done. In Jadassohn's case several of the tumors were excised, ground up into a "brei" and many cultures made on different media, though in vain. Like success also attended experiments with rabbits, guinea-pigs, doves, chickens, rats and a dog. But in working with apes the results were better. The first animal (*Cercopithecus sabeus*) was inoculated on the eyebrows with some of the "brei," and in forty-five days several growths appeared which eventually reached the size of small cherries. One of these was excised for further transmission to a *Rhesus*, and in fourteen days tumor growths were noted which finally reached a larger size than in the first animal. Lesions from the second ape were successfully transmitted to still a third animal (a *Rhesus*), where the incubation period was only seven days. This ape died suddenly, autopsy revealing nothing, so that further inoculations had to be made with the almost healed tumors from Ape 2, and they were unsuccessful, though done intravenously. Rabbits, guinea-pigs, rats, white and gray mice, chickens and doves were also further experimented on, but in vain. In all these apes the blood-picture was at all times normal, and neither in them nor in the man was it possible to find in the blood or in the red cells of the tissue fluids any of the inclusion-bodies that have been reported by Bassett-Smith,⁷ Galli-Valerio,¹⁶ DeVecchi⁹ and others, though practically all known parasite stains were used. Moreover, in none of the apes did the autopsy show changes that could in any way have been due to *Verruga peruviana*. The cutaneous lesions from both the man and the apes showed the same characteristic histological picture, which will be taken up more in detail in a later paper.¹⁷ Here it will be enough to say that the growths showed a marked vascular proliferation along with the presence of many free red blood-cells in the tissues. Many mono- and polymorphonuclear leukocytes, plasma cells and fibroblasts were noted in the tissues and peculiar lymph-vessels inclusion-areas, thus far imperfectly noted and described, were also seen. By the use of no known tissue parasitic stain was it possible to find any of the acid fast bacilli, cell-inclusion parasites or other organisms that have been described by different men. Odriozola says he has made examinations in two types of patients. In the first class, where there is a cutaneous

16. Galli-Valerio, B.: Observations microscopiques sur la Verruga peruana ou maladie de Carrion: Centralbl. f. Bakteriöl., etc., 1911, lviii, Part 1. Orig. p. 228.

17. A histological study will appear later in the *Journal of Cutaneous Diseases*.

eruption and no temperature, he has always had negative results. In the second type, with eruption and temperature, he has always found a small bacillus. In such classes of patients Biffi, DeVecchi, Barton and others have also found an organism closely related to the paratyphosus bacillus. Type B, and it may be that the negative results are due in this case to the fact that the patient, at least to our knowledge, at no time had any temperature or other especial symptoms of the "*Fièvre grave de Carrion*." Is it possible that Carrion could have been inoculated from a *Verruga peruviana* patient suffering also from a different disease, Oroya fever or "*Fièvre grave de Carrion*," and that he succumbed to the latter before the "*Eruption de Carrion*" had an opportunity to make its appearance? This question and many others in regard to the advisability of separating the affection into two clinical and distinct entities can only be solved by future study with large amounts of material at hand. However, I feel safe in making at least the following conclusions:

CONCLUSIONS

1. In a case of *Verruga peruviana*, *Eruption de Carrion*, there was success in inoculating the disease into apes to the third generation, further transmissions being hindered only from want of material.
2. The lesions from the man and the apes resembled each other very closely histologically, were granulomatous in type and had peculiar lymph-vessel inclusion-areas.
3. None of the organisms mentioned as specific for the disease were found either in the lesions from the patient or from the animals.

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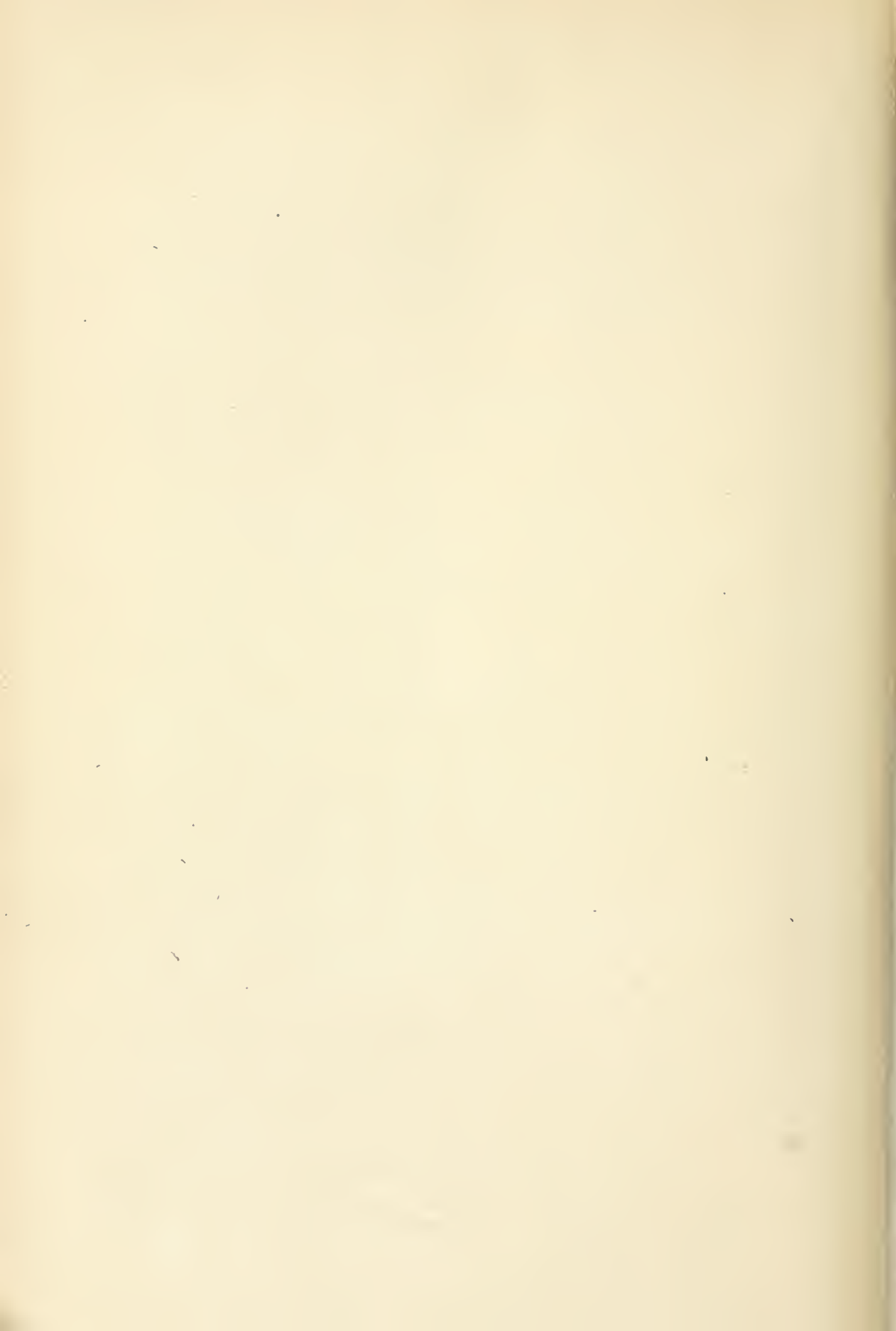
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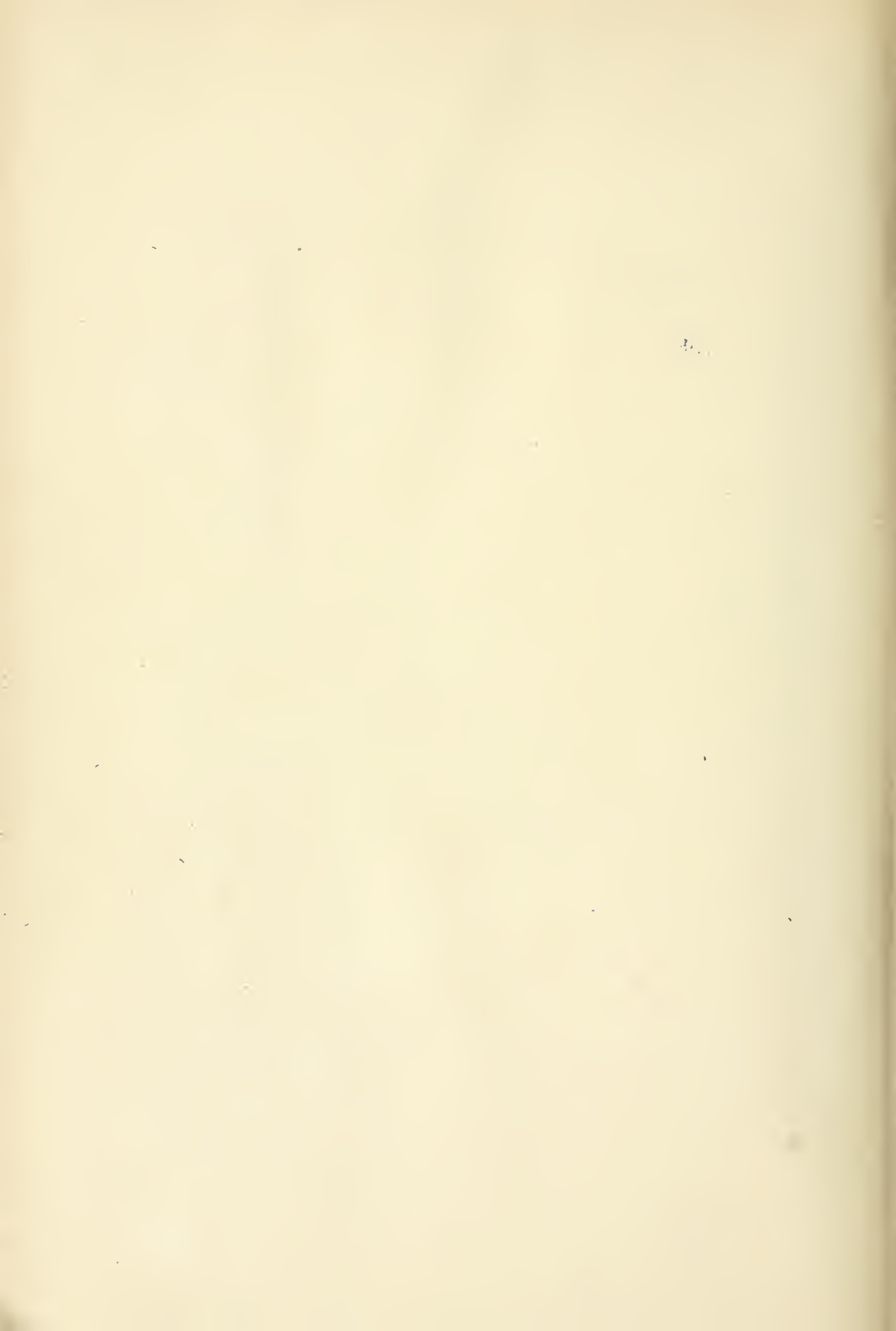
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